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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: Compounds having the formula or therapeutically acceptable salts thereof, are histone deacetylase (HDAC) inhibitors. Preparation of the compounds, compositions containing the compounds, and treatment of diseases using the compounds are disclosed.

INHIBITORS OF HISTONE DEACETYLASE

Technical Field

The present invention relates to compounds which are useful for inhibiting histone deacetylase (HDAC), methods of making the compounds, compositions containing the compounds, and methods of treatment using the compounds.

Background of the Invention

The organized packing of DNA in the eukaryotic nucleus plays an important role in the regulation of gene transcription. DNA's highly condensed state is a consequence of its wrapping into chromatin. The fundamental repeating structural unit of chromatin is the nucleosome, which consists of 146 bases of DNA wrapped around a complex of eight histone proteins, two molecules each of the core histones, H2A, H2B, H3, and H4. Each core histone octomer is comprised of several highly conserved structural motifs including a globular domain and an N-terminal tail domain that extends outside of the nucleosome. These histone N-terminal tails are enriched in basic amino acids, and are thought to mediate histone-DNA contacts through electrostatic interactions with DNA's negatively charged phosphate backbone. Based on the x-ray crystal structure of the nucleosome core particle, N-terminal histone tails also form contacts with the surface of histones of neighboring nucleosomes.

The capacity of histones to compact DNA is influenced by a number of post-translational modifications that occur on the N-terminal histone tails. One modification involves the reversible acetylation and deacetylation of the epsilon-amino group of lysine moieties found within the histone tails. The net level of acetylation of N-terminal histone tails is controlled by the activities of two families of enzymes, the histone acetyltransferases (HATs) and histone deacetylases (HDACs). The identification of coactivator complexes that possess intrinsic HAT activity strongly supports the connection between histone acetylation and transcriptional activation (Bioessays **1998**, 20, 615). Similarly, transcriptional repressor complexes have been shown to recruit HDACs to the promoter of target genes.

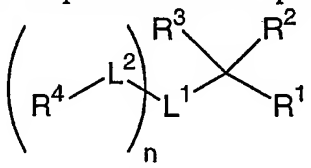
Several human cancers have been associated with malfunctions in HAT and HDAC activity. One example is the translocation of chromosomes 15 and 17 seen in the majority of acute promyelocytic leukemia patients. This translocation leads to the formation of a chimeric protein composed of the retinoic acid receptor fused to the PML transcription factor

(PML-RARa) (Mol. and Cell. Bio. **1998**, 18, 7176). The recruitment of HDACs by this fusion protein diminishes its responsiveness to retinoic acid resulting in inhibition of differentiation of hematopoietic cells, one of the characteristic features of this disease.

Inhibition of the action of HDACs causes a variety of cellular responses including the accumulation of hyperacetylated histones, altered gene expression, and cell cycle arrest. Antiproliferative and antitumor properties have also been described for compounds possessing HDAC inhibitory activity (J. Biol. Chem. **1999**, 274, 34940). While a number of natural product and synthetic HDAC inhibitors have been reported (J. Med.Chem. **1999**, 42, 3001; and PNAS, **1998**, 95, 3003), there still exists a need for inhibitors with improved profiles of activity.

Summary of the Invention

In its principle embodiment the present invention provides a compound of formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

n is 1 or 2;

L^1 is selected from the group consisting of alkenylene, alkylene, alkynylene, cycloalkylene, heteroalkylene, -(alkylene)-C(O)N(R^5)-(alkylene)-, -(alkylene)-O-(alkylene)-; wherein each group is drawn with its left-hand end being the end which attaches to L^2, and its right-hand end being the end which attaches to the carbon substituted with R^1, R^2, and R^3;

L^2 is selected from the group consisting of a bond, C_2 alkenylene, -O-, -S-, -SO_2-, -OC(O)NR^5-, -N(R^6)C(O)-, -C(O)N(R^6)-, -SO_2N(R^6)-, -N(R^6)SO_2-, -C=N-O-, -N(R^6)C(O)N(R^6)-, and -C(O)N(R^6)N(R^6)C(O)-;

wherein each group is drawn with its left-hand end being the end which attaches to R^4, and its right-hand end being the end which attaches to L^1;

R^1 is selected from the group consisting of alkanoyl, alkoxycarbonyl, aminocarbonyl, carboxy, haloalkyl, and heterocycle, wherein the heterocycle is selected from the group consisting of oxazolyl, dihydrooxazolyl, oxadiazolyl, and tetraazolyl;

R^2 and R^3 are hydroxy; or

R^2 and R^3 together are oxo;

R^4 is selected from the group consisting of alkoxyalkyl, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle, and (heterocycle)alkyl; and

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, and arylalkyl; or

R^4 and R^6, together with the nitrogen atom to which they are attached, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, piperidinyl, and thiomorpholinyl; wherein the morpholinyl, the piperazinyl, the piperidinyl, and the thiomorpholinyl can be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl and spiroheterocycle.

In another embodiment, the present invention discloses a compound according to Claim 1 wherein n is 2.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is heterocycle, wherein the heterocycle is selected from the group consisting of oxazolyl, dihydrooxazolyl, oxadiazolyl, and tetraazolyl; and L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is selected from the group consisting of alkoxycarbonyl and carboxy; and L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is alkanoyl; and L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl; and L^1 is -(alkylene)-O-(alkylene)-.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl, L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is selected from the group consisting of -O-, -S-, $-SO_2-$, and $-SO_2N(R_6)-$.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl, L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is selected from the group consisting of $-N(R^6)C(O)N(R^6)-$ and $-C(O)N(R^6)-$.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl, L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is selected from the group consisting of a bond, -C=N-O-, and $-N(R^6)C(O)CHC(O)N(R^5)(R^6)-$.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl, L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is $-N(R^6)C(O)-$.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is aminocarbonyl, L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is selected from the group consisting of $-N(R^6)C(O)N(R^6)-$ and $-C(O)N(R^6)N(R^6)C(O)-$.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; and L^1 is selected from the group consisting of alkenylene,

wherein the alkenylene is C_6 alkenylene; alkynylene, wherein the alkynylene is C_6 alkynylene; cycloalkylene; and -(alkylene)C(O)N(R^5)(alkylene)-.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is C_2 alkenylene.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is -OC(O)N(R^5)-.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; and L^2 is -O-.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; L^2 is -N(R^6)C(O)-; and R^4 is selected from the group consisting of alkoxyalkyl and alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; L^2 is -N(R^6)C(O)-; and R^4 is aryl.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; L^2 is -N(R^6)C(O)-; and R^4 is arylalkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; L^2 is -N(R^6)C(O)-; and R^4 is selected from the group consisting of cycloalkyl, heterocycle, and (heterocycle)alkyl.

In another embodiment, the present invention provides a compound of formula (I) wherein n is 1; R^1 is haloalkyl; L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene; L^2 is -N(R^6)C(O)-; and R^4 and R^6, together with the nitrogen atom to which they are attached, form a ring selected from the group consisting of morpholinyl, piperazinyl, piperidinyl, and thiomorpholinyl.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a therapeutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a method of inhibiting histone deacetylase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of formula (I), or a therapeutically acceptable salt thereof.

Detailed Description of the Invention

Compounds of the present invention are useful for the treatment of diseases in which histone deacetylase plays a role.

As used in the present specification the following terms have the meanings indicated:

The term "alkanoyl," as used herein, represents an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkenylene," as used herein, represents a divalent group of two to ten carbon atoms derived from a straight or branched chain hydrocarbon containing at least one double bond.

The term "C_2 alkenylene," as used herein, represents a divalent group of two carbon atoms containing a double bond.

The term "C_6 alkenylene", as used herein, represents a divalent group of six carbon atoms containing at least one double bond.

The term "alkoxy," as used herein, represents an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, represents an alkoxy group attached to the parent molecular moiety through an alkyl group.

The term "alkoxycarbonyl," as used herein, represents an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl," as used herein, represents a group of one to twelve carbon atoms derived from a straight or branched chain saturated hydrocarbon.

The term "alkylene," as used herein, represents a divalent group of one to ten carbon atoms derived from a straight or branched chain saturated hydrocarbon. The alkylene groups of the present invention can be optionally substituted with a hydroxy group.

The term "C_5-C_7 alkylene," as used herein, represents a divalent group of five to seven carbon atoms derived from a straight or branched chain saturated hydrocarbon. The C_5-C_7 alkylene groups of the present invention can be optionally substituted with a hydroxy group.

The term "C_6 alkylene," as used herein, represents a divalent group of six carbon atoms derived from a straight or branched chain saturated hydrocarbon. The C_6 alkylene groups of the present invention can be optionally substituted with a hydroxy group.

The term "alkylsulfanyl," as used herein, represents an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "alkylsulfonyl," as used herein, represents an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "alkynylene," as used herein, represents a divalent group of two to ten carbon atoms derived from a straight or branched chain hydrocarbon containing at least one

triple bond.

The term "C_6 alkynylene," as used herein, represents a divalent group of six carbon atoms derived from a straight or branched chain hydrocarbon containing at least one triple bond.

The term "amino," as used herein, represents $-NR^7R^8$, wherein R^7 and R^8 are independently selected from the group consisting of hydrogen, alkanoyl, alkyl, cycloalkyl, (cycloalkyl)alkyl, a nitrogen protecting group, and unsubstituted aryl.

The term "aminocarbonyl," as used herein, represents an amino group attached to the parent molecular moiety through a carbonyl group.

The term "aryl," as used herein, represents a phenyl group or a bicyclic or tricyclic fused ring system wherein one or more of the fused rings is a phenyl group. Bicyclic fused ring systems are exemplified by a phenyl group fused to a cycloalkyl group as defined herein, a cycloalkenyl group as defined herein, or another phenyl group. Tricyclic fused ring systems are exemplified by a bicyclic fused ring system fused to a cycloalkyl group as defined herein, a cycloalkenyl group as defined herein, or another phenyl group. Representative examples of aryl include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. Aryl groups having an unsaturated or partially saturated ring fused to an aromatic ring can be attached through the saturated or the unsaturated part of the group. The aryl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkanoyl, alkoxy, alkyl, alkylsulfanyl, alkylsulfonyl, amino, aminoalkoxy, a second aryl, arylalkoxy, arylalkyl, arylcarbonyl, aryloxy, arylsulfanyl, arylsulfonyl, carbonyloxy, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, heterocycle, (heterocycle)alkoxy, (heterocycle)alkyl, hydroxy, nitro, and oxo; wherein the second aryl, the aryl part of the arylalkoxy, the arylalkyl, the arylcarbonyl, the aryloxy, the arylsulfanyl, and the arylsulfonyl; the heterocycle; and the heterocycle part of the (heterocycle)alkyl can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkoxy, alkyl, alkylsulfanyl, alkylsulfonyl, amino, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "arylalkoxy," as used herein, represents an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkyl," as used herein, represents an aryl group attached to the parent molecular moiety through an alkyl group. The alkyl part of the arylalkyl groups of the present invention can be optionally substituted with one or two substituents independently selected from the group consisting of aminocarbonyl and aryl.

The term "arylcarbonyl," as used herein, represents an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, represents an aryl group attached to the parent molecular group through an oxygen atom.

The term "arylsulfanyl," as used herein, represents an aryl group attached to the parent molecular moiety through a sulfur atom.

The term "arylsulfonyl," as used herein, represents an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "carbonyl," as used herein, represents -C(O)-.

The term "carbonyloxy," as used herein, represents an alkanoyl group attached to the parent molecular moiety through an oxygen atom.

The term "carboxy," as used herein, represents $-CO_2H$.

The term "cyano," as used herein, represents -CN.

The term "cycloalkenyl," as used herein, represents a non-aromatic ring system having three to ten carbon atoms and one to three rings, wherein each five-membered ring has one double bond, each six-membered ring has one or two double bonds, each seven- and eight-membered ring has one to three double bonds, and each nine-to ten-membered ring has one to four double bonds. Examples of cycloalkenyl groups include cyclohexenyl, octahydronaphthalenyl, norbornylenyl, and the like.

The term "cycloalkyl," as used herein, represents a saturated monocyclic, bicyclic, or tricyclic hydrocarbon ring system having three to twelve carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, bicyclo(3.1.1)heptyl, adamantyl, and the like.

The term "(cycloalkyl)alkyl," as used herein, represents a cycloalkyl group attached to the parent molecular moiety through an alkyl group.

The term "cycloalkylene," as used herein represents a divalent group derived from a saturated monocyclic hydrocarbon ring system having three to twelve carbon atoms.

The term "halo," or "halogen," as used herein, represents F, Cl, Br, or I.

The term "haloalkoxy," as used herein, represents a haloalkyl group attached to the parent molecular group through an oxygen atom.

The term "haloalkyl," as used herein, represents an alkyl group substituted by one, two, three, or four halogen atoms.

The term "heteroalkylene," as used herein, represents a divalent group of two to eight atoms derived from a saturated straight or branched chain containing one or two heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein the remaining atoms are carbon. The heteroalkylene groups of the present invention can be attached through the carbon atoms or the heteroatoms in the chain.

The term "heterocycle," as used herein, represents a monocyclic, bicyclic, or tricyclic ring system wherein one or more rings is a four-, five-, six-, or seven-membered ring

containing one, two, or three heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from the group consisting of nitrogen, oxygen and sulfur. The 3- and 4-membered rings have no double bonds, the 5-membered ring has from 0-2 double bonds and the 6- and 7-membered rings have from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, a cycloalkenyl group, as defined herein, or another monocyclic heterocycle ring system. Representative examples of bicyclic ring systems include but are not limited to, benzimidazole, benzothiazole, benzothiophene, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like. Tricyclic rings systems are exemplified by any of the above bicyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, a cycloalkenyl group as defined herein, or another monocyclic heterocycle ring system. Representative examples of tricyclic ring systems include, but are not limited to, acridine, carbazole, carboline, dibenzofuran, dibenzothiophene, naphthofuran, naphthothiophene, oxanthrene, phenazine, phenoxathiin, phenoxazine, phenothiazine, thianthrene, thioxanthene, xanthene, and the like. Heterocycle groups can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the ring.

The heterocycle groups of the present invention can be optionally substituted with one, two, three, or four substituents independently selected from the group consisting of alkanoyl, alkoxy, alkyl, alkylsulfanyl, amino, aryl, arylalkoxy, arylalkyl, arylcarbonyl, aryloxy, arylsulfanyl, carbonyloxy, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, a second heterocycle, hydroxy, nitro, oxo, and spiroheterocycle; wherein the

second heterocycle can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkoxy, alkyl, amino, aminoalkoxy, cyano, halo, haloalkoxy, haloalkyl, a third heterocycle, hydroxy, and nitro. The third heterocycle can be further optionally substituted with one, two, or three substituents independently selected from the group consisting of alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, nitro, and oxo.

The term "(heterocycle)alkoxy," as used herein, represents a heterocycle group attached to the parent molecular moiety through an alkoxy group.

The term "(heterocycle)alkyl," as used herein, represents a heterocycle group attached to the parent molecular group through an alkyl group.

The term "hydroxy," as used herein, represents -OH.

The term "nitro," as used herein, represents $-NO_2$.

The term "nitrogen protecting group," as used herein, represents groups intended to protect an amino group against undesirable reactions during synthetic procedures. Common N-protecting groups comprise acyl groups such as acetyl, benzoyl, 2-bromoacetyl, 4-bromobenzoyl, tert-butylacetyl, carboxaldehyde, 2-chloroacetyl, 4-chlorobenzoyl, α-chlorobutyryl, 4-nitrobenzoyl, o-nitrophenoxyacetyl, phthalyl, pivaloyl, propionyl, trichloroacetyl, and trifluoroacetyl; sulfonyl groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, benzyloxycarbonyl (Cbz), tert-butyloxycarbonyl (Boc), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, and the like.

The term "oxo," as used herein, represents (=O).

The term "spiroheterocycle," as used herein, represents a heteroalkylene diradical, each end of which is attached to the same carbon atom of the parent molecular moiety. Examples of spiroheterocycles include dioxolanyl, tetrahydrofuranyl, pyrrolidinyl, and the like.

The term "sulfonyl," as used herein, represents $-SO_2-$.

The present compounds can also exist as therapeutically acceptable prodrugs. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The term "prodrug," refers to compounds which are rapidly transformed in vivo to parent compounds of formula (I) for example, by hydrolysis in blood.

The compounds of the present invention can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible, which are suitable for treatment of diseases without undue toxicity, irritation, and

allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting an amino group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, amino groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

In addition to the compounds of the present invention and their pharmaceutically acceptable salts, the invention is further directed, where applicable, to unsolvated as well as solvated forms of the compounds (e.g., hydrated forms) having the ability to inhibit HDAC.

Because carbon-carbon double bonds exist in the present compounds, the invention contemplates various geometric isomers and mixtures thereof resulting from the arrangement of substituents around these carbon-carbon double bonds. It should be understood that the invention encompasses both isomeric forms, or mixtures thereof, which possess the ability to inhibit histone deacetylase. These substituents are designated as being in the E or Z

configuration wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon double bond, and the term "Z" represents higher order substituents on the same side of the carbon-carbon double bond.

In accordance with methods of treatment and pharmaceutical compositions of the invention, the compounds can be administered alone or in combination with other HDAC inhibitors. When using the compounds, the specific therapeutically effective dose level for any particular patient will depend upon factors such as the disorder being treated and the severity of the disorder; the activity of the particular compound used; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the route of administration; the rate of excretion of the compound employed; the duration of treatment; and drugs used in combination with or coincidently with the compound used. The compounds can be administered orally, parenterally, osmotically (nasal sprays), rectally, vaginally, or topically in unit dosage formulations containing carriers, adjuvants, diluents, vehicles, or combinations thereof. The term "parenteral" includes infusion as well as subcutaneous, intravenous, intramuscular, and intrasternal injection.

Parenterally administered aqueous or oleaginous suspensions of the compounds can be formulated with dispersing, wetting, or suspending agents. The injectable preparation can also be an injectable solution or suspension in a diluent or solvent. Among the acceptable diluents or solvents employed are water, saline, Ringer's solution, buffers, monoglycerides, diglycerides, fatty acids such as oleic acid, and fixed oils such as monoglycerides or diglycerides.

The inhibitory effect of parenterally administered compounds can be prolonged by slowing their absorption. One way to slow the absorption of a particular compound is by administering injectable depot forms comprising suspensions of crystalline, amorphous, or otherwise water-insoluble forms of the compound. The rate of absorption of the compound is dependent on its rate of dissolution which is, in turn, dependent on its physical state. Another way to slow absorption of a particular compound is by administering injectable depot forms comprising the compound as an oleaginous solution or suspension. Yet another way to slow absorption of a particular compound is by administering injectable depot forms comprising microcapsule matrices of the compound trapped within liposomes, microemulsions, or biodegradable polymers such as polylactide-polyglycolide, polyorthoesters or polyanhydrides. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled.

Transdermal patches can also provide controlled delivery of the compounds. The rate of absorption can be slowed by using rate controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In these solid dosage forms, the active compound can optionally comprise diluents such as sucrose, lactose, starch, talc, silicic acid, aluminum hydroxide, calcium silicates, polyamide powder, tableting lubricants, and tableting aids such as magnesium stearate or microcrystalline cellulose. Capsules, tablets and pills can also comprise buffering agents, and tablets and pills can be prepared with enteric coatings or other release-controlling coatings. Powders and sprays can also contain excipients such as talc, silicic acid, aluminum hydroxide, calcium silicate, polyamide powder, or mixtures thereof. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons or substitutes therefor.

Liquid dosage forms for oral administration include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs comprising inert diluents such as water. These compositions can also comprise adjuvants such as wetting, emulsifying, suspending, sweetening, flavoring, and perfuming agents.

Topical dosage forms include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and transdermal patches. The compound is mixed under sterile conditions with a carrier and any needed preservatives or buffers. These dosage forms can also include excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Suppositories for rectal or vaginal administration can be prepared by mixing the compounds with a suitable non-irritating excipient such as cocoa butter or polyethylene glycol, each of which is solid at ordinary temperature but fluid in the rectum or vagina. Ophthalmic formulations comprising eye drops, eye ointments, powders, and solutions are also contemplated as being within the scope of the present invention.

The total daily dose of the compounds administered to a host in single or divided doses can be in amounts from about 0.1 to about 200 mg/kg body weight or preferably from about 0.25 to about 100 mg/kg body weight. Single dose compositions can contain these amounts or submultiples thereof to make up the daily dose.

Preferred compounds of the present invention include, but are not limited to:

Compounds of formula (I) wherein R^1 is aminocarbonyl. Most preferred compounds of the present invention include compounds of formula (I) wherein R^1 is $-C(O)NHCH_3$.

Determination of Biological Activity

Activity assay for human histone deacetylases

Compounds of the present invention were tested in one of two assays designed to measure histone deacetylase inhibition. Conditions for each of the two assays are described below.

Assay 1

Nuclear histone deacetylase enzymes were partially purified from human erythroleukemia K562 cells by MonoQ sepharose chromatography (Proceedings of the National Academy of Sciences of the United States of America **1999**, 96, 4592). The substrates, (^{3}H)-labeled nuclear histones, were prepared from K562 cells by incubation of cells with (^{3}H)-acetic acid in the presence of 3 mM trichostatin A and isolated by dounce homogenization, acid extraction of isolated nuclei, and acetone precipitation (*J. Biol. Chem.* **1990**, 265, 17174). The standard assay consisted of 3-6 μg of histone deacetylase incubated with 5-10 μg (~10,000 cpm) of labeled-nuclear histones for 1 hour at 37 °C in a 50 mL reaction volume. Inhibitor was added 15 minutes prior to substrate addition. The reaction was terminated by the addition of 1M HCl/0.16M acetic acid (50 mL) and ethyl acetate (500 mL). The mixture was inverted for 30 seconds and the phases were separated by centrifugation (1000 rpm for 2 minutes). An aliquot of the organic phase was removed and counted in a liquid scintillation spectrophotometer. IC_{50} values were determined by log-logit linear regression of the dose response data.

Assay 2

A white DYNEX Microfluor 2 plate was treated with 70 μL buffer (containing 10 mM Tris HCl, 1 mM $MgCl_2$, 10 mM $CaCl_2$ at pH 8.0 containing 2% glycerol and 0.015% Tween-80); 12 μL inhibitor (compound) solution in 10% DMSO/buffer; and 18 μL HDAC solution diluted in buffer (the amount of HDAC is adjusted to cleave approximately 10% of the acetyl-lysine from the peptide substrate in a 30 minute reaction). The plate was mixted and preincubated for 30 minutes at room temperature, treated with 20 μL of a 4.8μM solution of substrate (a histone mimetic sequence containing one acetyl lysine group, prepared as a 0.24 mM DMSO stock solution), and incubated for 30 minutes. Each well was treated with 30 μL of a solution of endoproteinase-Lys-C containing trichostatin-A (endoproteinase-Lys-C was added at a concentration of 10 ng/well and the final concentration of trichlostatin-A was 7 μM in 150 μL). The buffer used for the quench was 10 mM Hepes/5 mM EDTA, adjusted to pH 8.0 with NaOH, and contains 2% glycerol and 0.015% Tween-80.

The wells of the plate were read by a fluorescence plate reader (fmax, Molecular Devices) with filters of 544 nm (excitation) and 590 nm (emission). The background fluorescence was determined by addition of trichostatin-A to certain wells before addition of enzyme, and was substracted from the readings of the other wells. The extent of inhibition of the enzyme by the inhibitors was calculated from the readings of wells containing an inhibitor and those of control (containing no inhibitor). The IC_{50} was determined by a log/logit analysis of the inhibitor concentration and inhibition data.

The compounds of the present invention were found to inhibit histone deacetylase with inhibitory potencies between 1 nM and 50 μM. Preferred compounds inhibited histone deacetylase with inhibitory potencies between 1 nM and 1 μM and most preferred compounds inhibited histone deacetylase with inhibitory potencies between 1 nM and 100 nM. Thus, the compounds of the present are useful for treating diseases in which histone deacetylase plays a role.

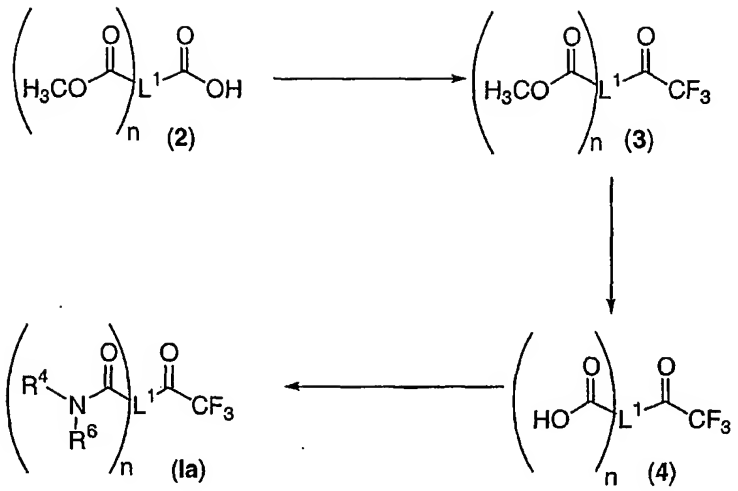
Synthetic Methods

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: DMAP for 4-dimethylaminopyridine; CDI for 1,1'-carbonyldiimidazole; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DCC for 1,3-dicyclohexylcarbodiimide; HOBt for 1-hydroxybenzotriazole hydrate; DMF for N,N-dimethylformamide; NMP for N-methylpyrrolidinone; THF for tetrahydrofuran; MTBE for methyl tert-butyl ether; DMSO for dimethylsulfoxide; OAc for acetate; DME for 1,2-dimethoxyethane; DEAD for diethyl azodicarboxylate; DIAD for diisopropyl azodicarboxylate; LAH for lithium aluminum hydride; NMM for N-methylmorpholine; TBAF for tetrabutylammonium fluoride; DBU for 1,8-diazabicyclo(5.4.0)undec-7-ene; pTsOH for p-toluenesulfonic acid; DBN for 1,5-diazabicyclo(4.3.0)non-5-ene; LDA for lithium diisopropylamide; KHMDS for potassium hexamethyldisilazide; PDC for pyridinium dichromate; NBS for N-bromosuccinimide; TBS for tert-butyldimethylsilyl, and mCPBA for m-chloroperoxybenzoic acid.

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. The groups n, L^1, L^2, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above unless otherwise noted below.

This invention is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes. Preparation of the compounds of the invention by metabolic processes include those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

Scheme 1

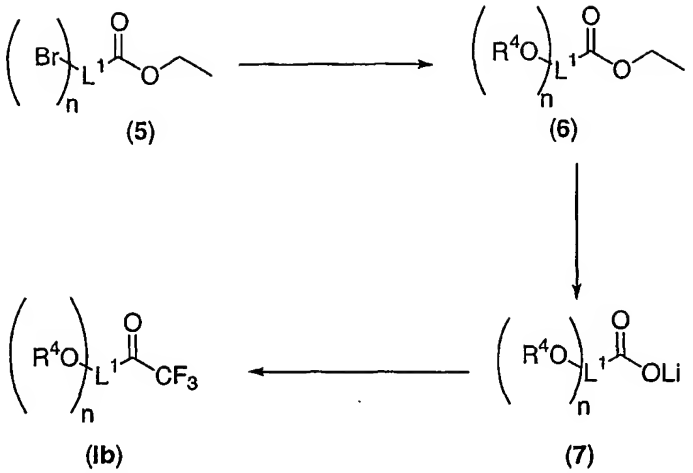


As shown in Scheme 1, compounds of formula (**2**) can be converted to compounds of formula (**3**) by treatment with a base and trifluoroacetic anhydride. Examples of bases used in these reactions include sodium hydride, lithium hexamethyldisilazide, pyridine, and mixtures thereof. Representative solvents used in these reactions include dichloromethane, carbon tetrachloride, and chloroform. The reaction is conducted at about -10 °C to about 5 °C and reaction times are typically about 2 to about 24 hours.

Compounds of formula (**3**) can be converted to compounds of formula (**4**) by hydrolysis methods known to those of ordinary skill in the art.

Conversion of compounds of formula (**4**) to compounds of formula (**Ia**) can be accomplished by treatment with an appropriately substituted amine (HNR^4R^6) in the presence of a base and a coupling agent. Examples of bases include NMM, DMAP, and triethylamine. Representative coupling agents include CDI, EDCI, DCC, HOBt, and mixtures thereof. Solvents typically used in these reactions include DMF, NMP, and dioxane. The reaction is conducted at about 20 °C to about 40 °C and reaction times are typically about 12 to about 24 hours.

Scheme 2



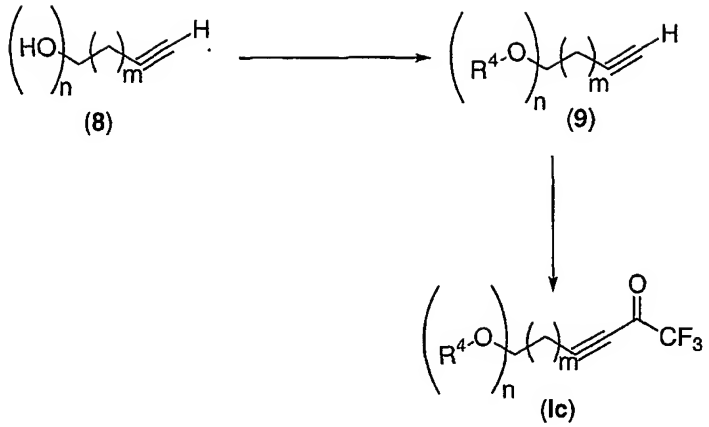
As shown in Scheme 2, compounds of formula (**5**) can be converted to compounds of formula (**6**) by treatment with an appropriately substituted alcohol (R^4OH) in the presence of a base. Example of bases include Cs_2CO_3, K_2CO_3, and Na_2CO_3. Representative solvents include DMF, NMP, and dioxane. The reaction is conducted at about 20 °C to about 40 °C and reaction times are typically about 12 to about 24 hours.

Compounds of formula (**6**) can be converted to compounds of formula (7) by hydrolysis methods known to those of ordinary skill in the art.

Conversion of compounds of formula (7) to compounds of formula (**Ib**) can be accomplished by treatment with trifluoroacetic anhydride. Solvents commonly used in these reactions include dichloromethane, chloroform, and carbon tetrachloride. The reaction is conducted at about 20 °C to about 40 °C and reaction times are typically about 2 to about 4 hours.

Compounds of formula (**Ib**) wherein L^1 is alkynylene or alkenylene can be readily converted to compounds of formula (**Ib**) wherein L^1 is alkenylene or cycloalkylene, respectively, by methods such as cyclopropanation and reduction, well-known to those of ordinary skill in the art.

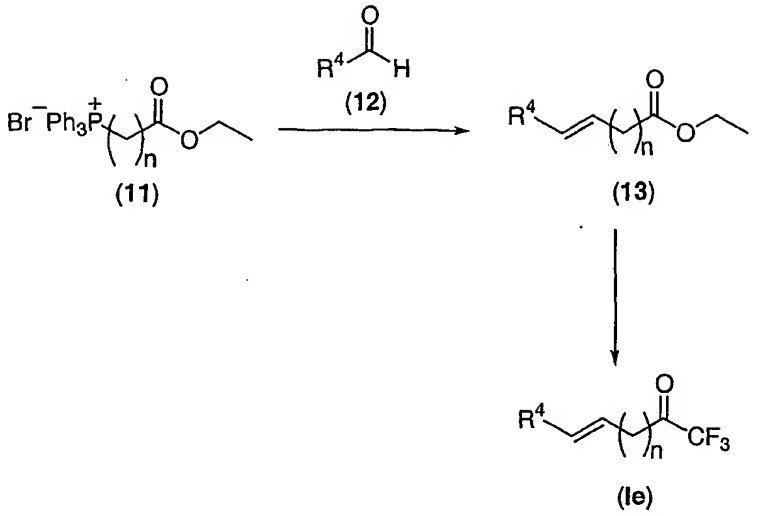
Scheme 3



As shown in Scheme 3, compounds of formula (**8**) (m is a positive integer between 1 and 7) can be treated with an appropriately substituted alcohol (R^4OH) in the presence of a trialkylphosphine or triarylphosphine and a diazo compound to provide compounds of formula (**9**). Representative trialkylphosphines include tributylphosphine and trimethylphosphine; representative triarylphosphines include triphenylphosphine and tri-o-tolylphosphine; and representative diazo compounds include DEAD and DIAD. Solvents commonly used in these reactions include THF, diethyl ether, and methyl tert-butyl ether. The reaction is conducted at about -5 °C to about 30 °C, and typical reaction times are about 12 to about 24 hours.

Compounds of formula (**9**) can be converted to compounds of formula (**Ic**) by treatment with base followed by an ester of trifluoroacetic acid. Representative bases include n-butyllithium, tert-butyllithium, and lithium hexamethyldisilazide. Examples of solvents used in these reactions include THF, diethyl ether, and methyl tert-butyl ether. The reaction is conducted at about -78 °C to about 30 °C and typical reaction times are about 18 to about 24 hours.

Scheme 4



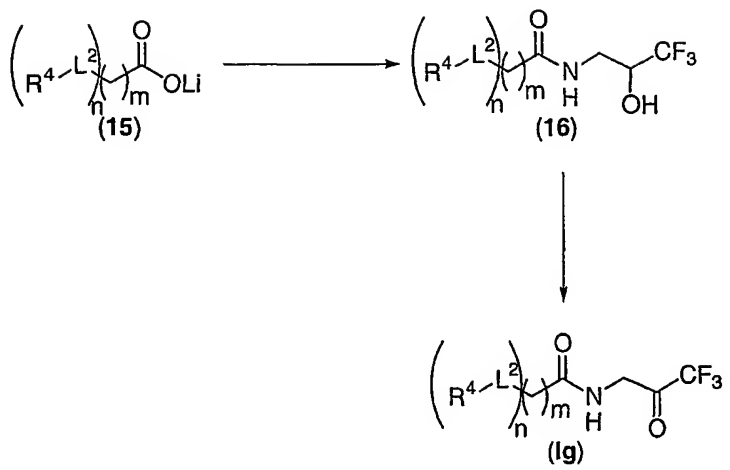
As shown in Scheme 4, compounds of formula (**11**) (n is a positive integer between 1 and 8) can be treated with compounds of formula (**12**) and base to provide compounds of formula (**13**). Examples of bases used in these reactions include potassium tert-butoxide and sodium tert-butoxide. Representative solvents include THF, methyl tert-butyl ether, and diethyl ether. The reaction temperature is about -5 °C to about 25 °C and reaction times are typically about 1 to about 3 hours.

Compounds of formula (**13**) can be converted to compounds of formula (**Ie**) following the procedures described in Scheme 2.

Scheme 5

As shown in Scheme 5, compounds of formula (**14**) can be converted to compounds of formula (**If**) by treatment with oxalyl chloride, followed by treatment with trifluoroacetic anhydride and base. Examples of bases include pyridine, triethylamine, and diisopropylethylamine. Representative solvents include dichloromethane, 1,2-dichloroethane, and carbon tetrachloride. The reaction temperature is about -60 °C to about 25 °C and reaction times are typically about 2 hours to about 4 hours.

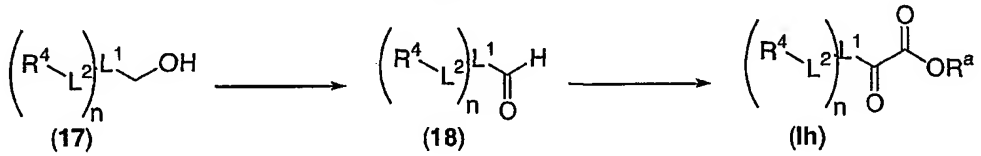
Scheme 6



As shown in Scheme 6, compounds of formula (**15**) (prepared from the corresponding ester according to the procedures described in Scheme 2) can be converted to compounds of formula (**16**) by treatment with 2-hydroxy-2-(trifluoromethyl)ethylamine (prepared as described in *J. Org. Chem.* **1995**, *60*, 41) using the conditions described in Scheme 2.

Conversion of compounds of formula (**16**) to compounds of formula (**Ig**) can be accomplished by oxidation, using a variety of procedures known to those of ordinary skill in the art.

Scheme 7

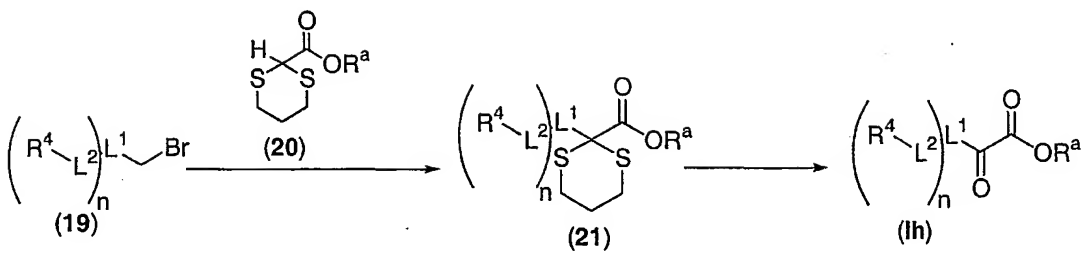


As shown in Scheme 7, compounds of formula (**17**) can be oxidized to compounds of formula (**18**) by numerous methods well-known to those of ordinary skill in the art, such as the Swern oxidation and the Dess-Martin oxidation.

Compounds of formula (**18**) can be converted to compounds of formula (**Ih**) (R^a is alkyl) by treatment with an alkyl ester of (dimethoxyphosphoryl)(tetrahydro-2H-pyran-2-yloxy)acetic acid (which can be prepared following the procedure described in *Tet. Lett.* **1981**, *22*, 663-666) in the presence of base. Representative bases include DBU, DBN, and DMAP. Examples of solvents used in these reactions include acetonitrile, THF, and diethyl ether. The reaction is conducted at about 0 °C to about 25 °C and reaction times are typically about 1 to about 3 hours.

Compounds of formula (**Ih**) where R^a is alkyl can be intraconverted to compounds of formula (**Ih**) where R^a is hydrogen by the hydrolysis methods shown in Scheme 1.

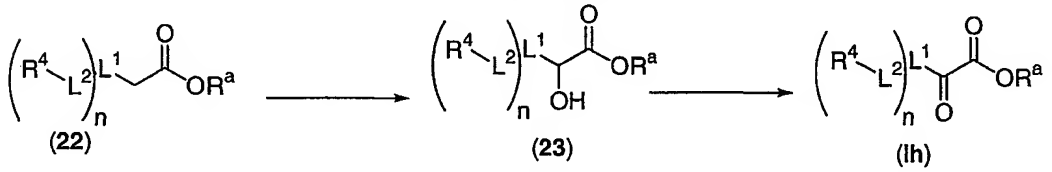
Scheme 8



Scheme 8 shows an alternative synthesis of compounds of formula (**Ih**). Compounds of formula (**19**) can be reacted with compounds of formula (**20**) (R^a is alkyl) in the presence of base to provide compounds of formula (**21**). Representative bases include NaH, KH, and LiHMDS. Examples of solvents used in these reactions include DMF, THF, and diethyl ether. The reaction is conducted at about -78 °C to about 0 °C and reaction times are typically about 12 to about 24 hours.

Compounds of formula (**21**) can be converted to compounds of formula (**Ih**) by treatment with a variety of deprotection reagents such as NBS, known to those of ordinary skill in the art.

Scheme 9

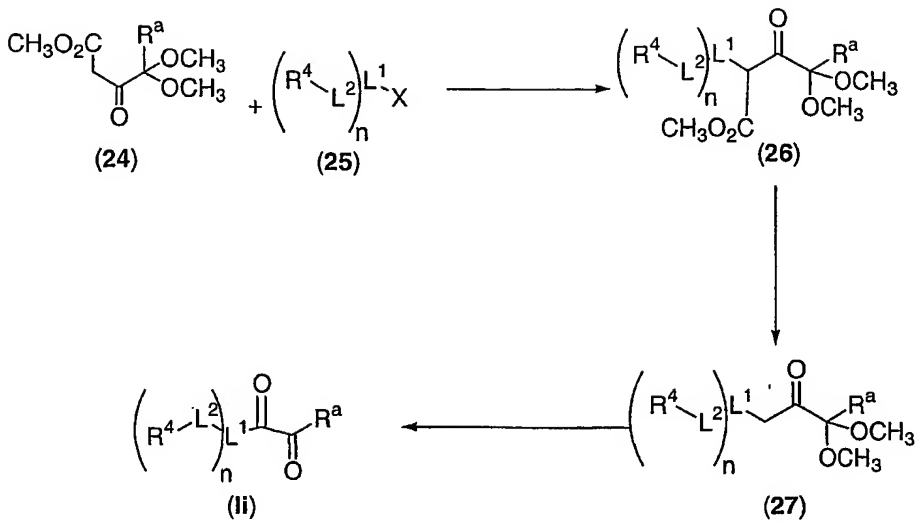


Another route to compounds of formula (**Ih**) is shown in Scheme 9. Compounds of formula (**22**) can be converted to compounds of formula (**23**) by treatment with 2-benzenesulfonyl-3-phenyl-oxaziridine (prepared according to the procedure described in J. Org. Chem. **1992**, 47, 1774-1775) in the presence of base. Representative bases include KHMDS, LiHMDS, and LDA. Examples of solvents used in these reactions include THF, MTBE, and diethyl ether. The reaction is conducted at about -78 °C to about 0 °C and reaction times are typically about 30 minutes to about 2 hours.

Compounds of formula (**23**) can be converted to compounds of formula (**Ih**) by treatment with a variety of oxidation reagents, such as PDC, known to those of ordinary skill in the art.

Compounds of formula (**Ih**) can be reacted with various primary or secondary amines to form the corresponding ketoamides using procedures well-known to those of ordinary skill in the art.

Scheme 10



As shown in Scheme 10, compounds of formula (**24**) (R^a is alkyl) can be treated sequentially with a base and with compounds of formula (**25**) to provide compounds of formula (**26**). Representative bases include sodium hydride, potassium hydride, lithium hexamethyldisilazide, and lithium diisopropylamide. Examples of solvents used in these reactions include DMF, THF, MTBE, and diethyl ether. The reaction is typically conducted at about –78 °C to about 25 °C for about 2 to about 48 hours.

Compounds of formula (**26**) can be converted to compounds of formula (**27**) by treatment with a hydrolyzing agent. Representative hydrolyzing agents include sodium hydroxide and lithium hydroxide. Examples of solvents used in these reactions include methanol and ethanol. The reaction is conducted at about 25 °C to about 75 °C for about 1 to about 6 hours.

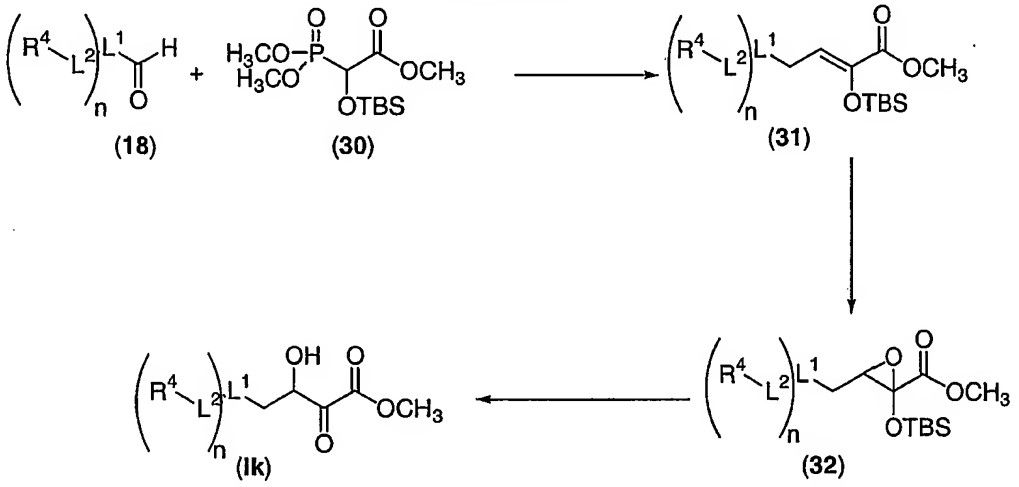
Conversion of compounds of formula (**27**) to compounds of formula (**Ii**) can be accomplished by treatment with a deprotecting agent such as HCl, trifluoroacetic acid, p-toluenesulfonic acid, or acetic acid. The reaction is conducted at about 0 °C to about 35 °C for about 1 to about 12 hours.

Scheme 11

Scheme 11 shows the conversion of compounds of formula (**29**) to compounds of formula (**Ij**). Treatment of compounds of formula (**29**) with a stabilized anion of a heterocycle (generated by deprotonation with a strong base such as n-butyllithium at

-78 °C followed by treatment with zinc chloride) in the presence of stoichiometric copper (such as copper iodide) gives compounds of formula (**Ij**). Examples of solvents used in these reactions include THF, diethyl ether, and MTBE. The reaction is conducted at about -78 °C to about 0 °C and reaction times are typically about 1 to about 3 hours.

Scheme 12

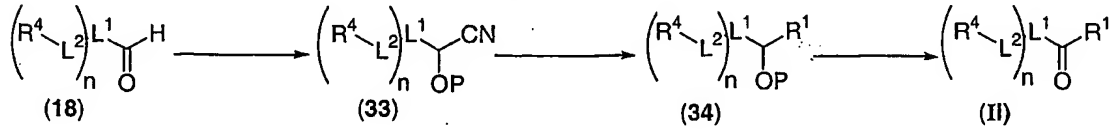


As shown in Scheme 12, compounds of formula (**18**) (prepared according to the methods described in Scheme 7) can be reacted with compounds of formula (**30**) in the presence of base and lithium chloride to provide compound of formula (**31**). Examples of bases include DBU, diisopropylethylamine, and sodium hydride. Representative solvents include THF, MTBE, and dioxane. The reaction is conducted at about 0 to about 23 °C for about 1 to about 16 hours.

Compounds of formula (**31**) can be reacted with an oxidizing agent to produce compounds of formula (**32**). Representative oxidizing agents include mCPBA with potassium fluoride, and t-butyl peroxide with n-butyllithium. Examples of solvents include dichloromethane, THF, and chloroform. The reaction is conducted at about 0 to about 23 °C for about 8 to about 16 hours.

Conversion of compounds of formula (**32**) to compounds of formula (**Ik**) can be accomplished by treatment with triethylamine trihydrofluoride. Examples of solvents used in this reaction include acetonitrile, tetrahydrofuran, and toluene. The reaction is conducted at about 0 to about 23 °C for about 8 to about 16 hours.

Scheme 13



As shown in Scheme 13, compounds of formula (**18**) can be reacted with KCN to provide compounds of formula (**33**) (P is H). Examples of solvents used in these reactions include THF, water, and mixtures thereof. The reaction is typically conducted at about 10 °C to about 35 °C for about 12 to about 72 hours.

Compounds of formula (**33**) where P is H can be converted to compounds of formula (33) where P is a hydroxy protecting group can be accomplished by means known to those of ordinary skill in the art.

Compounds of formula (**33**) where P is H can be converted to compounds of formula (**34**) (where R is dihydrooxazolyl by treatment with acetyl chloride in ethanol and chloroform followed by treatment with ethanolamine and triethylamine in dichloromethane, followed by treatment with p-toluenesulfonic acid in chloroform. Reaction temperatures are typically between 20 °C and 62 °C and reaction times are typically about 3 to about 24 hours.

Compounds of formula (**33**) can be converted to compounds of formula (**33**) where P is a hydroxy protecting group can be converted to compounds of formula (**34**) by treatment with sodium azide and ammonium chloride in DMF. Reaction temperatures are typically about 80 °C to about 153 °C for about 1 to about 6 hours.

Compounds of formula (**34**) where P is a hydroxy protecting group can be converted to compounds of formula (**34**) where P is hyrogen my methods known to those of ordinary skill in the art.

Conversion of compounds of formula (**34**) to compounds of formula (**II**) can be accomplished by oxidation using methods known to those of oridinary skill in the art.

The present invention will now be described in connection with certain preferred embodiments which are not intended to limit its scope. On the contrary, the present invention covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include preferred embodiments, will illustrate the preferred practice of the present invention, it being understood that the examples are for the purposes of illustration of certain preferred embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Compounds of the invention were named by ACD/ChemSketch version 5.0 (developed by Advanced Chemistry Development, Inc., Toronto, ON, Canada) or were given names which appeared to be consistent with ACD nomenclature.

Example 1

9,9,9-trifluoro-8-oxo-N-phenylnonanamide

Example 1A

methyl 9,9,9-trifluoro-8-oxononanoate

A suspension of NaH (750 mg, 29.7 mmol) in dichloromethane (150 mL) at 0 °C was treated dropwise with 8-methoxy-8-oxooctanoic acid (5.10 g, 27.1 mmol), stirred until gas evolution ceased, treated with trifluoroacetic anhydride (34.2 g, 163 mmol), stirred for 10 minutes, and treated with pyridine (18.9 g, 225 mmol). The mixture was warmed to room temperature, stirred for 1.5 hours, poured over ice (400 g), and warmed to room temperature. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 1:1 dichloromethane/hexanes to provide 2.68 g (41%) of the desired product. MS (ESI(-)) m/e 239 $(M-H)^-$.

Example 1B

9,9,9-trifluoro-8-oxononanoic acid

A solution of Example 1A (1.40 g, 5.8 mmol) in THF (25 mL) at room temperature was treated with 2M LiOH (35 mL, 70 mmol), stirred for 18 hours, and concentrated. The remaining solution was adjusted to pH 2 with 1N HCl and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to provide 1.28 g (98%) of the desired product of sufficient purity for subsequent use. MS (ESI(-)) m/e 225 $(M-H)^-$.

Example 1C

9,9,9-trifluoro-8-oxo-N-phenylnonanamide

A solution of Example 1B (256 mg, 1.1 mmol), aniline (112 mg, 1.2 mmol), HOBt (179 mg, 1.3 mmol) and N-methylmorpholine (221 mg , 2.2 mmol) in DMF (3 mL) at room temperature was treated with EDCI (254 mg, 1.3 mmol), stirred for 18 hours, poured into water (50 mL), and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 7:3 hexanes/ethyl acetate to provide 273 mg (82%) of the desired product. MS (ESI(+)) m/e 302 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.58 (d, 2H), 7.35-7.30 (m, 2H), 7.01 (td, 1H), 2.86 (t, 2H), 2.29 (t, 2H), 1.65-1.50 (m, 4H), 1.47-1.23 (m, 4H); Anal. Calcd for $C_{15}H_{18}F_3NO_2$: C, 59.79; H, 6.02; N, 4.65. Found: C, 59.62; H, 5.91; N, 4.51.

Example 2

8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-2-octanone

Example 2A

ethyl 7-((1,1'-biphenyl)-4-yloxy)heptanoate

A mixture of ethyl 7-bromoheptanoate (53.1 g, 15.4 mmol), (1,1'-biphenyl)-4-ol (2.61 g, 15.3 mmol), and Cs_2CO_3 (5.49 g, 16.9 mmol) in DMF (50 mL) at room temperature was stirred for 18 hours, poured into ice water (400 mL), and filtered to provide 4.87 g (98%) of the desired product. MS (ESI(+)) m/e 327 $(M+H)^+$.

Example 2B

lithium 7-((1,1'-biphenyl)-4-yloxy)heptanoate

A solution of Example 2A (4.86 g, 14.9 mmol) in THF (15 mL) at room temperature was treated with 2M LiOH (25 mL, 50 mmol), heated to 80 °C for 2 hours, cooled to room temperature, filtered, and dried to provide 4.30g (95%) of the desired product. MS (ESI(-)) m/e 297 $(M-Li)^-$.

Example 2C

8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-2-octanone

A solution of trifluoroacetic anhydride (2.14 g, 10.2 mmol) in dichloromethane (16 mL) at room temperature was treated with Example 2B (502 mg, 1.66 mmol), and pyridine (1.12 g, 13.4 mmol), stirred for 3 hours, and quenched with water (5 mL). The mixture was stirred for 10 minutes, poured into water (75 mL), and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with dichloromethane to provide 235 mg (40%) of the desired product. MS (ESI(-)) m/e 349 $(M-H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.45-7.40 (m, 2H), 7.37-7.33 (m, 1H), 7.00 (d, 2H), 4.00 (t, 2H), 2.89 (t, 2H), 1.75-1.68 (m, 2H), 1.65-1.55 (m, 2H), 1.47-1.36 (m, 4H); Anal. Calcd for $C_{20}H_{21}F_3O_2$: C, 68.56; H, 6.04. Found: C, 68.35; H, 6.10.

Example 3

4'-((8,8,8-trifluoro-7-oxooctyl)oxy)(1,1'-biphenyl)-4-carbonitrile

The desired product was prepared by substituting 4'-hydroxy(1,1'-biphenyl)-4-carbonitrile for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(-)) m/e 374 $(M-H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, 2H), 7.83 (d, 2H), 7.70 (d, 2H), 7.05 (d, 2H), 4.03 (t, 2H), 2.89 (t, 2H), 1.76-1.69 (m, 2H), 1.62-1.57 (m, 2H), 1.49-1.36 (m, 4H); Anal. Calcd for $C_{21}H_{20}F_3NO_2$: C, 67.19; H, 5.37; N, 3.73. Found: C, 67.24; H, 5.29; N, 3.58.

Example 4

9-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-2-nonanone

The desired product was prepared by substituting ethyl 8-bromooctanoate for ethyl 7-bromoheptanoate in Example 2. MS (ESI(-)) m/e 363 $(M-H)^-$; ^{1}H NMR (300 MHz, DMSO-

d_6) δ 7.62-7.55 (m, 4H), 7.45-7.39 (m, 2H), 7.33-7.27 (m, 1H), 7.01 (d, 2H), 4.00 (t, 2H), 2.88 (t, 2H), 1.75-1.68 (m, 2H), 1.60-1.55 (m, 2H), 1.43-1.32 (m, 6H); Anal. Calcd for $C_{21}H_{23}F_3O_2$: C, 69.22; H, 6.36. Found: C, 69.12; H, 6.28.

Example 5

7-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-2-heptanone

The desired product was prepared by substituting ethyl 6-bromohexanoate for ethyl 7-bromoheptanoate in Example 2. MS (ESI(-)) m/e 335 $(M-H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62-7.57 (m, 4H), 7.45-7.40 (m, 2H), 7.33-7.27 (m, 1H), 7.01 (d, 2H), 4.01 (t, 2H), 2.92 (t, 2H), 1.78-1.71 (m, 2H), 1.71-1.62 (m, 2H), 1.51-1.43 (m, 2H); Anal. Calcd for $C_{19}H_{19}F_3O_2$: C, 67.85; H, 5.69. Found: C, 67.82; H, 5.69.

Example 6

9,9,9-trifluoro-8-oxo-N-(4-pyridinyl)nonanamide

A mixture of Example 1B (50 mg, 0.22 mmol), HOBt (30 mg, 0.22 mmol), carbodiimide PS resin (720 mg), and 4-aminopyridine (25 mg, 0.27 mmol) in DMF (5 mL) at room temperature was agitated in a Quest 210 parallel synthesizer for 18 hours, treated with trisamine PS resin (220 mg), and agitated for 2 hours. The solution was decanted, the resin was rinsed with dichloromethane, and the combined solutions were concentrated. The concentrate was purified by preparative HPLC with a gradient system of 0 to 95% over 10 min of CH_3CN (containing 0.1%TFA) in water to provide the desired product. MS (ESI(+)) m/e 303 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.64 (d, 2H), 7.96 (d, 2H), 2.87 (t, 2H), 2.46 (t, 2H), 1.63-1.55 (m, 4H), 1.34-1.29 (m, 4H); Anal. Calcd for $C_{16}H_{20}F_3NO_2 \cdot CF_3CO_2H \cdot 0.1H_2O$: C, 45.96; H, 4.39; N, 6.70. Found: C, 45.60; H, 4.30; N, 6.70.

Example 7

N-benzyl-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting benzylamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 316 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32-8.25 (m, 1H), 7.33-7.28 (m, 2H), 7.26-7.20 (m, 3H), 4.25 (d, 2H), 2.85 (t, 2H), 2.13 (t, 2H), 1.64-1.46 (m, 4H), 1.33-1.28 (m, 4H); Anal. Calcd for $C_{16}H_{20}F_3NO_2 \cdot 0.75H_2O$: C, 58.44; H, 6.59; N, 4.26. Found: C, 58.18; H, 6.45; N, 4.05.

Example 8

9,9,9-trifluoro-8-oxo-N-(3-pyridinylmethyl)nonanamide

The desired product was prepared by substituting 3-pyridinylmethanamine for 4-

aminopyridine in Example 6. MS (ESI(+)) m/e 317 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61-8.58 (m, 2H), 8.44-8.40 (m, 1H), 7.97-7.94 (m, 1H), 7.62 (dd, 1H), 4.34 (d, 2H), 2.85 (t, 2H), 2.14 (t, 2H), 1.62-1.51 (m, 4H), 1.28-1.22 (m, 4H).

Example 9

9,9,9-trifluoro-8-oxo-N-(2-phenylethyl)nonanamide

The desired product was prepared by substituting 2-phenylethanamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 330 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (m, 1H), 7.31-7.26 (m, 2H), 7.21-7.18 (m, 3H), 3.25 (q, 2H), 2.85 (t, 2H), 2.69 (t, 2H), 2.02 (t, 2H), 1.58-1.43 (m, 4H), 1.30-1.18 (m, 4H).

Example 10

9,9,9-trifluoro-N-(4-methoxyphenyl)-8-oxononanamide

The desired product was prepared by substituting 4-methoxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 332 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.47 (d, 2H), 6.85 (d, 2H), 3.71 (s, 3H), 2.88-2.84 (m, 2H), 2.28-2.23 (m, 2H), 1.64-1.52 (m, 4H), 1.34-1.25 (m, 4H); Anal. Calcd for $C_{16}H_{20}F_3NO_3 \cdot 0.7H_2O$: C, 55.87; H, 6.27; N, 4.07. Found: C, 55.64; H, 6.13; N, 3.88.

Example 11

9,9,9-trifluoro-N-(3-methoxyphenyl)-8-oxononanamide

The desired product was prepared by substituting 3-methoxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 332 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.30 (br s, 1H), 7.21-7.09 (m, 2H), 6.61-6.59 (m, 1H), 3.71 (s, 3H), 2.87 (t, 2H), 2.28 (t, 2H), 1.62-1.51 (m, 4H), 1.36-1.25 (m, 4H); Anal. Calcd for: $C_{16}H_{20}F_3NO_3 \cdot 0.6H_2O$: C, 56.17; H, 6.25; N, 4.09. Found: C, 55.81; H, 6.04; N, 3.91.

Example 12

9,9,9-trifluoro-N-(2-methoxyphenyl)-8-oxononanamide

The desired product was prepared by substituting 2-methoxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 332 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.91 (d, 1H), 7.08-7.00 (m, 2H), 6.91-6.85 (m, 1H), 3.82 (s, 3H), 2.87 (t, 2H), 2.36 (t, 2H), 1.64-1.51 (m, 4H), 1.34-1.26 (m, 4H).

Example 13

9,9,9-trifluoro-8-oxo-N-(3-phenylpropyl)nonanamide

The desired product was prepared by substituting 3-phenyl-1-propanamine for 4-

aminopyridine in Example 6. MS (ESI(+)) m/e 344 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.78 (br t, 1H), 7.30-7.25 (m, 2H), 7.20-7.14 (m, 3H), 3.03 (dd, 2H), 2.85 (t, 2H), 2.58-2.53 (m, 2H), 2.05 (t, 2H), 1.72-1.43 (m, 6H), 1.31-1.21 (m, 4H); Anal. Calcd for $C_{18}H_{24}F_3NO_2 \cdot H_2O$: C, 59.82; H, 7.25; N, 3.88. Found: C, 59.42; H, 6.94; N, 3.80.

Example 14

N-(4-(dimethylamino)phenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-dimethylaminoaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 345 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (br s, 1H), 7.47 (br d, 2H), 6.95-6.83 (br s, 1H), 6.64-6.54 (br s, 1H), 2.92 (br s, 6H), 2.86 (t, 2H), 2.25 (t, 2H), 1.65-1.52 (m, 4H), 1.33-1.25 (m, 4H).

Example 15

N-(1,3-benzodioxol-5-yl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 1,3-benzodioxol-5-amine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 346 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (br s, 1H), 7.31-7.30 (br s, 1H), 6.95-6.92 (m,1H), 6.82 (d, 1H), 5.96 (s, 2H), 2.87 (t, 2H), 2.25 (t, 2H), 1.62-1.52 (m, 4H), 1.35-1.26 (m, 4H); Anal. Calcd for $C_{16}H_{18}F_3NO_4$: C, 55.65; H, 5.25; N, 4.06. Found: C, 55.18; H, 5.00; N, 4.51.

Example 16

9-(1,4-dioxa-8-azaspiro(4.5)dec-8-yl)-1,1,1-trifluoro-9-oxo-2,2-nonanediol

The desired product was prepared by substituting 1,4-dioxa-8-azaspiro(4.5)decane for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 352 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.65-6.48 (br s, 2H), 3.89 (s, 4H), 3.51-3.44 (m, 4H), 2.30 (t, 2H), 1.62-1.56 (m, 4H), 1.55-1.34 (m, 6H), 1.32-1.21 (m, 4H).

Example 17

N-(1,1'-biphenyl)-4-yl-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (1,1'-biphenyl)-4-amine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 378 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.70-7.59 (m, 6H), 7.46-7.42 (m, 2H), 7.35-7.30 (m, 1H), 2.88 (t, 2H), 2.35-2.30 (m, 2H), 1.67-1.52 (m, 4H), 1.38-1.29 (m, 4H); Anal. Calcd for $C_{21}H_{22}F_3NO_2 \cdot 0.2H_2O$: C, 66.20; H, 5.93; N, 3.68. Found: C, 66.06; H, 5.89; N, 3.67.

Example 18

N-(1,1'-biphenyl)-3-yl-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (1,1'-biphenyl)-3-amine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 378 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.92 (s, 1H), 7.61-7.56 (m, 3H), 7.50-7.45 (m, 2H), 7.40-7.30 (m, 3H), 2.87 (t, 2H), 2.32 (t, 2H), 1.68-1.52 (m, 4H), 1.39-1.27 (m, 4H).

Example 19

N-(1,1'-biphenyl)-2-yl-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (1,1'-biphenyl)-2-amine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 378 $(M+H)^+$;^{1}H NMR (300 MHz, DMSO-d_6) δ 9.18 (s, 1H), 7.42-7.30 (m, 9H), 2.85 (t, 2H), 2.13-2.11 (m, 2H), 1.63-1.33 (m, 4H), 1.28-1.14 (m, 4H).

Example 20

N-(4-cyclohexylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-cyclohexylaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 384 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.46 (d, 2H), 7.11 (d, 2H), 2.86 (t, 2H), 2.49-2.38 (m, 1H), 2.26 (t, 2H), 1.82-1.65 (m, 5H), 1.64-1.51 (m, 4H), 1.41-1.25 (m, 9H). Anal. Calcd for $C_{21}H_{28}F_3NO_2 \cdot 0.3H_2O$: C, 64.86; H, 7.41; N, 3.60. Found: C, 64.69; H, 7.16; N, 3.36.

Example 21

9,9,9-trifluoro-8-oxo-N-(4-(1-piperidinyl)phenyl)nonanamide4

The desired product was prepared by substituting 4-(1-piperidinyl)aniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 385 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) d 10.14-9.84 (br s, 1H), 7.68-7.55 (br s, 2H), 6.66-6.56 (br s, 2H), 2.87 (t, 2H), 2.51 (br s, 4H), 2.33-2.26 (m, 2H), 1.84-1.71 (m, 4H), 1.64-1.52 (m, 5H), 1.49-1.37 (m, 1H), 1.33-1.25 (m, 4H).

Example 22

9,9,9-trifluoro-N-(4-(4-morpholinyl)phenyl)-8-oxononanamide

The desired product was prepared by substituting 4-(4-morpholinyl)aniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 387 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.45 (d, 2H), 6.19 (d, 2H), 3.75-3.72 (m, 4H), 3.17-3.04 (m, 4H), 2.86 (t, 2H), 2.25 (t, 2H), 1.63-1.50 (m, 4H), 1.36-1.24 (m, 4H).

Example 23

N-((1S)-1-benzyl-2-(methylamino)-2-oxoethyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (2S)-2-amino-N-methyl-3-phenylpropanamide for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 387 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.03-7.98 (m, 1H), 7.92-7.84 (m, 1H), 7.31-7.13 (m, 5H), 4.49-4.38 (m, 1H), 2.99-2.93 (m, 1H), 2.82 (t, 2H), 2.71 (dd, 1H), 2.56 (d, 3H), 2.02 (t, 2H), 1.55-1.44 (m, 2H), 1.36-1.24 (m, 2H), 1.24-1.11 (m, 2H), 1.11-1.06 (m, 2H); Anal. Calcd for $C_{19}H_{25}F_3N_2O_3 \cdot 0.1H_2O$: C, 58.78; H, 6.54; N, 7.22. Found: C, 58.40; H, 6.57; N, 7.24.

Example 24

N-benzhydryl-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting benzhydrylamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 392 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.70 (d, 1H), 7.35-7.20 (m, 10H), 6.11 (d, 1H), 2.83 (t, 2H), 2.20 (t, 2H), 1.58-1.49 (m, 4H), 1.32-1.21 (m, 4H); Anal. Calcd for $C_{22}H_{24}F_3NO_2$: C, 67.51; H, 6.18; N, 3.58. Found: C, 67.22; H, 6.13; N, 3.57.

Example 25

9,9,9-trifluoro-8-oxo-N-(3-pyridinyl)nonanamide

The desired product was prepared by substituting 3-aminopyridine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 321 $(M+H_2O+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.13 (br s, 1H), 8.77-8.76 (m, 1H), 8.27-8.25 (m, 1H), 8.08-8.04 (m, 1H), 7.40-7.36 (m, 1H), 2.87 (t, 2H), 2.34 (t, 2H), 1.65-1.56 (m, 4H), 1.36-1.29 (m, 4H).

Example 26

N-cyclohexyl-9,9,9-trifluoro-8,8-dihydroxynonanamide

The desired product was prepared by substituting cyclohexylamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 308 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.61 (d, 1H), 6.60 (s, 2H), 3.56-3.43 (m, 1H), 2.01 (t, 2H), 1.74-1.36 (m, 12H), 1.34-1.03 (m, 8H); Anal. Calcd for $C_{15}H_{24}F_3NO_2 \cdot 0.9H_2O$: C, 55.68; H, 8.04; N, 4.33. Found: C, 55.60; H, 8.19; N, 4.41.

Example 27

9,9,9-trifluoro-N-(4-hydroxyphenyl)-8-oxononanamide

The desired product was prepared by substituting 4-hydroxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 318 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.56 (s, 1H), 9.11 (s, 1H), 7.34 (d, 2H), 6.64 (d, 2H), 2.86 (t, 2H), 2.23 (t, 2H), 1.62-1.52 (m, 4H), 1.34-1.26 (m, 4H); Anal. Calcd for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.73; H, 5.94; N, 4.38.

Example 28

9,9,9-trifluoro-N-(4-fluorophenyl)-8-oxononanamide

The desired product was prepared by substituting 4-fluoroaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 320 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.59 (dd, 2H), 7.12 (t, 2H), 2.87 (t, 2H), 2.28 (t, 2H), 1.65-1.52 (m, 4H), 1.36-1.26 (m, 4H); Anal. Calcd for $C_{15}H_{17}F_4NO_2$: C, 56.43; H, 5.37; N, 4.39. Found: C, 56.73; H, 5.94; N, 4.38.

Example 29

N-(3-cyanophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3-cyanoaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 325 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.11-8.09 (m, 1H), 7.78 (dt, 1H), 7.54-7.47 (m, 2H), 2.87 (t, 2H), 2.33 (t, 2H), 1.66-1.53 (m, 4H), 1.34-1.27 (m, 4H); Anal. Calcd for $C_{16}H_{17}F_3N_2O_2 \cdot 0.5H_2O$: C, 58.89; H, 5.25; N, 8.58. Found: C, 57.64; H, 5.29; N, 7.91.

Example 30

N-(4-chlorophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-chloroaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 336 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.61 (d, 2H), 7.33 (d, 2H), 2.89-2.84 (m, 2H), 2.30 (t, 2H), 1.64-1.53 (m, 4H), 1.35-1.24 (m, 4H); Anal. Calcd for $C_{15}H_{17}ClF_3NO_2 \cdot 0.9H_2O$: C, 51.19; H, 5.38; N, 3.98. Found: C, 51.07; H, 5.44; N, 3.99.

Example 31

N-(4-acetylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 1-(4-aminophenyl)ethanone for 4-aminopyridine in Example 6. MS (APCI(+)) 344 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.91 (d, 2H), 7.71 (d, 2H), 2.87 (t, 2H,), 2.50 (s, 3H), 2.35 (t, 2H), 1.63-1.54 (m, 4H), 1.34-1.28 (m, 4H).

Example 32

N-(2-adamantyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 2-adamantanamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 360 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.60 (d, 1H), 3.82 (d, 1H), 2.85 (t, 2H), 2.13 (d, 2H), 1.99-1.94 (m, 2H), 1.84-1.67 (m,

10H), 1.59-1.43 (m, 6H), 1.34-1.23 (m, 4H); Anal. Calcd for $C_{19}H_{28}F_3NO_2 \cdot 0.1CF_3COOH$: C, 62.19; H, 7.64; N, 3.78. Found: C, 62.64; H, 7.01; N, 3.44.

Example 33

9,9,9-trifluoro-8-oxo-N-(4-(trifluoromethyl)phenyl)nonanamide

The desired product was prepared by substituting 4-trifluoromethylaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 370 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.79 (d, 2H), 7.65 (d, 2H), 2.87 (t, 2H), 2.34 (t, 2H), 1.64-1.57 (m, 4H), 1.35-1.29 (m, 4H).

Example 34

N-(3,4-dichlorophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3,4-dichloroaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 370 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.99 (d, 1H), 7.54 (d, 1H), 7.48-7.45 (dd, 1H), 2.86 (t, 2H), 2.31 (t, 2H), 1.64-1.52 (m, 4H), 1.34-1.28 (m, 4H).

Example 35

N-(4-bromophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-bromoaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 380 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.56 (d, 2H), 7.46 (d, 2H), 2.87 (t, 2H), 2.30 (t, 2H), 1.64-1.53 (m, 4H), 1.34-1.26 (m, 4H); Anal. Calcd for $C_{15}H_{17}BrF_3NO_2 \cdot 0.9H_2O$: C, 45.45; H, 4.78; N, 3.53. Found: C, 45.37; H, 4.54; N, 3.38.

Example 36

N-(4-benzylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-benzylaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 392 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.77 (s, 1H), 7.48 (d, 2H), 7.30-7.25 (m, 2H), 7.21-7.17 (m, 3H), 7.12 (d, 2H), 3.87 (s, 2H), 2.87 (t, 2H), 2.26 (t, 2H), 1.63-1.50 (m, 4H), 1.34-1.26 (m, 4H); Anal. Calcd for $C_{22}H_{24}F_3NO_2$: C, 67.51; H, 6.18; N, 3.58. Found: C, 67.36; H, 5.90; N, 3.44.

Example 37

9,9,9-trifluoro-8-oxo-N-(4-phenoxyphenyl)nonanamide

The desired product was prepared by substituting 4-phenoxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 394 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-

d_6) δ 9.87 (s, 1H), 7.59 (d, 2H), 7.35 (dd, 2H), 7.12-7.06 (m, 1H), 6.99-6.59 (m, 4H), 2.87 (t, 2H), 2.29 (t, 2H), 1.66-1.52 (m, 4H), 1.48-1.26 (m, 4H); Anal. Calcd for $C_{21}H_{22}F_3NO_3$: C, 64.11; H, 5.64; N, 3.56. Found: C, 64.01; H, 5.61; N, 3.51.

Example 38

9,9,9-trifluoro-8,8-dihydroxy-N-(9-oxo-9H-fluoren-2-yl)nonanamide

The desired product was prepared by substituting 2-amino-9H-fluoren-9-one for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 404 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.95 (br s, 1H), 7.71-7.68 (m, 3H), 7.60-7.55 (m, 2H), 7.43-7.28 (m, 1H), 6.61 (s, 2H), 2.33 (t, 2H), 1.65-1.59 (m, 4H), 1.49-1.39 (m, 2H), 1.36-1.28 (m, 4H); Anal. Calcd for $C_{22}H_{20}F_3NO_3 \cdot 0.7H_2O$: C, 63.52; H, 5.18; N, 3.37. Found: C, 63.24; H, 4.77; N, 3.28.

Example 39

N-(4-(benzyloxy)phenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-(benzyloxy)aniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 408 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.49-7.32 (m, 7H), 6.93 (d, 2H), 5.05 (s, 2H), 2.86 (t, 2H), 2.25 (t, 2H), 1.63-1.52 (m, 4H), 1.34-1.28 (m, 4H).

Example 40

9,9,9-trifluoro-N-(3-methoxypropyl)-8-oxononanamide

The desired product was prepared by substituting 3-methoxy-1-propanamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 298 $(M+H)^+$.

Example 41

9,9,9-trifluoro-N-isopentyl-8-oxononanamide

The desired product was prepared by substituting 3-methyl-1-butanamine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 296 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (br m, 1H), 3.07-3.00 (m, 2H), 2.85 (t, 2H), 2.02 (t, 2H), 1.62-1.36 (m, 5H), 1.30-1.20 (m, 6H), 0.85 (d, 6H).

Example 42

N-(4'-cyano(1,1'-biphenyl)-3-yl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3'-amino(1,1'-biphenyl)-4-carbonitrile for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 403 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.01 (s, 1H), 7.94 (d, 2H), 7.81 (d, 2H), 7.61 (app d, 1H),

7.46-7.37 (m, 2H), 2.87 (t, 2H), 2.33 (t, 2H), 1.60-1.55 (m, 4H), 1.34 (m, 4H); Anal. Calcd for $C_{22}H_{21}F_3N_2O_2$: C, 65.66; H, 5.26; N, 6.96. Found: C, 65.50; H, 5.37; N, 7.04.

Example 43

N-(3-(benzyloxy)phenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3-(benzyloxy)aniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 408 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.73 (s, 1H), 7.48-7.26 (m, 6H), 7.21-7.07 (m, 2H), 6.70-6.65 (m, 1H), 5.06 (s, 2H), 2.86 (t, 2H), 2.28 (t, 2H), 1.59-1.55 (m, 4H), 1.33-1.28 (m, 4H); Anal. Calcd for $C_{22}H_{24}F_3NO_3$: C, 64.86; H, 5.94; N, 3.44. Found: C, 65.06; H, 5.95; N, 3.53.

Example 44

9,9,9-trifluoro-8-oxo-N-(3-phenoxyphenyl)nonanamide

The desired product was prepared by substituting 3-phenoxyaniline for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 394 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.42-7.27 (m, 5H), 7.15 (t, 1H), 7.02 (d, 2H), 6.67 (dt, 1H), 2.86 (t, 2H), 2.26 (t, 2H), 1.62-1.50 (m, 4H), 1.34-1.24 (m, 4H); Anal. Calcd for $C_{21}H_{22}F_3NO_3 \cdot 0.2H_2O$: C, 63.53; H, 5.69; N, 3.53. Found: C, 63.42; H, 5.62; N, 3.33.

Example 45

N-(3-benzoylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (3-aminophenyl)(phenyl)methanone for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 404 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.01 (s, 1H), 7.90 (dt, 1H), 7.75-7.66 (m, 3H), 7.60-7.54 (m, 2H), 7.48 (t, 1H), 7.39 (d, 1H), 2.86 (t, 2H), 2.31 (t, 2H), 1.63-1.52 (m, 4H), 1.34-1.25 (m, 4H); Anal. Calcd for $C_{22}H_{22}F_3NO_3 \cdot 0.2H_2O$: C, 64.60; H, 5.52; N, 3.42. Found: C, 64.46; H, 5.34; N, 3.47.

Example 46

9,9,9-trifluoro-8-oxo-N-(4-phenyl-1,3-thiazol-2-yl)nonanamide

The desired product was prepared by substituting 4-phenyl-1,3-thiazol-2-amine for 4-aminopyridine in Example 6. MS (ESI(+)) m/e 385 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 12.21 (s, 1H), 7.89 (d, 2H), 7.59 (s, 1H), 7.45-7.40 (m, 2H), 7.35-7.29 (m, 1H), 2.87 (t, 2H), 2.47 (t, 2H), 1.64-1.54 (m, 4H), 1.35-1.29 (m, 4H); Anal. Calcd for $C_{18}H_{19}F_3N_2O_2S$: C, 56.24; H, 4.98; N, 7.29. Found: C, 55.99; H, 4.94; N, 6.96.

Example 47

8-(3-bromophenoxy)-1,1,1-trifluoro-2-octanone

The desired product was prepared by substituting 3-bromophenol for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(-)) m/e 351 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.23 (t, 1H), 7.13-7.08 (m, 2H), 6.96-6.92 (m, 1H), 3.97 (t, 2H), 2.88 (t, 2H), 1.74-1.65 (m, 2H), 1.63-1.54 (m, 2H), 1.46-1.29 (m, 4H); Anal. Calcd for $C_{14}H_{16}BrF_3O_2 \cdot 0.2H_2O$:C, 47.13; H, 4.63. Found: C, 46.75; H, 4.75.

Example 48

1,1,1-trifluoro-8-(3-(4-pyridinyl)phenoxy)-2-octanone

The desired product was prepared by substituting 3-(4-pyridinyl)phenol for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(+)) m/e 352 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.62 (d, 2H), 7.71 (d, 2H), 7.42 (t, 1H), 7.36-7.31 (m, 2H), 7.05-7.02 (m, 1H), 4.06 (t, 2H), 2.89 (t, 2H), 1.77-1.60 (m, 2H), 1.68-1.58 (m, 2H), 1.49-1.30 (m, 4H); Anal. Calcd for $C_{19}H_{20}F_3NO_2 \cdot HCl \cdot 2.3H_2O$: C, 53.16; H, 6.01; N, 3.26. Found: C, 52.80; H, 5.99; N, 3.03.

Example 49

8-(4-bromophenoxy)-1,1,1-trifluoro-2-octanone

The desired product was prepared by substituting 4-bromphenol for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(-)) m/e 351 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.42 (d, 2H), 6.89 (d, 2H), 3.94 (t, 2H), 2.87 (t, 2H), 1.72-1.65 (m, 2H), 1.62-1.54 (m, 2H), 1.46-1.30 (m, 4H); Anal. Calcd for $C_{14}H_{16}BrF_3O_2$: C, 47.61; H, 4.57. Found: C, 47.88; H, 4.39.

Example 50

1,1,1-trifluoro-8-(4-phenoxyphenoxy)-2-octanone

The desired product was prepared by substituting 4-phenoxyphenol for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(-)) m/e 365 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.36-7.32 (m, 2H), 7.09-7.03 (m, 1H), 6.99-6.88 (m, 6H), 3.94 (t, 2H), 2.88 (t, 2H), 1.73-1.64 (m, 2H), 1.61-1.54 (m, 2H), 1.40-1.35 (m, 4H); Anal. Calcd for $C_{20}H_{21}F_3O_3$: C, 65.57; H, 5.78. Found: C, 65.26; H, 5.64.

Example 51

8-((1,1'-biphenyl)-3-yloxy)-1,1,1-trifluoro-2-octanone

The desired product was prepared by substituting (1,1'-biphenyl)-3-ol for (1,1'-biphenyl)-4-ol in Example 2. MS (ESI(-)) m/e 349 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.66 (d, 2H), 7.48-7.45 (m, 2H), 7.39-7.33 (m, 2H), 7.22-7.16 (m, 1H), 7.17-7.16 (m, 1H), 6.94-6.91 (m, 1H), 4.05-4.02 (m, 2H), 2.89 (t, 2H), 1.74 (m, 2H), 1.62-1.58 (m, 2H), 1.50-1.33 (m, 4H); Anal. Calcd for $C_{20}H_{21}F_3O_2$: C, 68.56; H, 6.04;. Found: C, 68.64; H, 6.08.

Example 52

9,9,9-trifluoro-8-oxo-N-(4'-(trifluoromethoxy)(1,1'-biphenyl)-3-yl)nonanamide

The desired product was prepared by substituting 4'-(trifluoromethoxy)(1,1'-biphenyl)-3-amine for aniline in Example 1. MS (DCI) m/e 462 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.94 (s, 1H), 7.63 (d, 2H), 7.57 (d, 1H), 7.47 (d, 2H), 7.38 (d, 1H), 7.34 (d, 1H), 2.86 (t, 2H), 2.33 (t, 2H), 1.68-1.50 (m, 4H), 1.40-1.25 (m, 4H); Anal. Calcd for $C_{22}H_{21}NO_3F_6$: C, 57.26; H, 4.58; N, 3.03. Found: C, 57.03; H, 4.65; N, 2.92.

Example 53

9,9,9-trifluoro-8-oxo-N-(3-(3-pyridinyl)phenyl)nonanamide

The desired product was prepared by substituting 3-(3-pyridinyl)aniline for aniline in Example 1. MS (DCI) m/e 379 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.0 (s, 1H), 8.82 (s, 1H), 8.58 (d, 1H), 8.00 (d, 1H), 7.95 (s, 1H), 7.64 (d, 1H), 7.53-7.31 (m, 3H), 2.86 (t, 2H), 2.33 (t, 2H), 1.69-1.52 (m, 4H), 1.41-1.20 (m, 4H); Anal. Calcd for $C_{20}H_{21}N_2O_2F_3 \cdot 0.5H_2O$: C, 62.01; H, 5.72; N, 7.23. Found: C, 61.98; H, 5.73; N, 7.05.

Example 54

9,9,9-trifluoro-N-(4'-(methylsulfanyl)(1,1'-biphenyl)-3-yl)-8-oxononanamide

Example 54A

N-(3-bromophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3-bromoaniline for aniline in Example 1. MS (ESI(+)) m/e 381 $(M+H)^+$.

Example 54B

9,9,9-trifluoro-N-(4'-(methylsulfanyl)(1,1'-biphenyl)-3-yl)-8-oxononanamide

A mixture of Example 54A (308 mg, 0.81 mmol), 4-(methylsulfanyl)phenyl-boronic acid (150 mg, 0.89 mmol), $Pd(OAc)_2$ (9.1 mg, 0.04 mmol), tri-o-tolylphosphine (24.4 mg, 0.08 mmol), and 2M Na_2CO_3 (2 mL, 2mmol) in DME (5 mL) was heated to 80 °C for 3 hours, treated with additional Pd $(OAc)_2$ (9 mg), tri-o-tolylphosphine (24 mg), and 3-(methylsulfanyl)phenyl-boronic acid (75 mg), heated for 3 hours, cooled to room temperature, and partitioned between diethyl ether and water. The aqueous phase was extracted with diethyl ether and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 7:3 hexanes/ethyl acetate to provide 164 mg (48%) of the desired product. MS (ESI(-)) m/e 422 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.94 (s,

1H), 7.90 (s, 1H), 7.55 (d, 3H), 7.42-7.22 (m, 4H), 2.86 (t, 2H), 2.49 (s, 3H), 2.33 (t, 2H), 1.68-1.51 (m, 4H), 1.36-1.27 (m, 4H); Anal. Calcd for $C_{22}H_{24}NO_2F_3S$: C, 62.39; H, 5.71; N, 3.31. Found: C, 63.18; H, 5.60; N, 2.75.

Example 55

N-(3'-amino(1,1'-biphenyl)-3-yl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3-aminophenylboronic acid for 4-(methylsulfanyl)phenylboronic acid in Example 54. MS (ESI(-)) m/e 391 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.87 (s, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 7.09 (t, 1H), 6.78 (dd, 1H), 6.72 (d, 1H), 6.56 (d, 1H), 5.17 (s, 2H), 2.87 (t, 2H), 2.34 (t, 2H), 1.67-1.52 (m, 4H), 1.38-1.27 (m, 4H); Anal. Calcd for $C_{21}H_{23}N_2O_2F_3$: C, 64.28; H, 5.91; N, 7.14. Found: C, 63.95; H, 5.99; N, 6.91.

Example 56

9,9,9-trifluoro-N-(4'-(methylsulfonyl)(1,1'-biphenyl)-3-yl)-8-oxononanamide

A suspension of Example 54B (85 mg, 0.2 mmol) in a 2:1 mixture of methanol/water (10 mL) at room temperature was treated with $NaHCO_3$ (42 mg, 0.5 mmol) and oxone (10 mL), stirred for 18 hours, and partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was recrystallized from ethyl acetate/hexane to provide 56 mg (62%) of the desired product. MS (ESI(-)) m/e 454 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.03 (d, 3H), 7.86 (d, 2H), 7.64 (d, 1H), 7.48-7.38 (m, 2H), 3.27 (s, 3H), 2.87 (t, 2H), 2.33 (t, 2H), 1.67-1.52 (m, 4H), 1.38-1.27 (m, 4H); Anal. Calcd for $C_{22}H_{24}NO_4F_3S \cdot 0.5H_2O$: C, 56.89; H, 5.42; N, 3.02. Found: C, 56.80; H, 5.47; N, 2.82.

Example 57

N-(4'-cyano(1,1'-biphenyl)-3-yl)-8,8,8-trifluoro-7-oxooctanamide

The desired product was prepared by substituting methyl 8,8,8-trifluoro-7-oxooctanoate and 3'-amino(1,1'-biphenyl)-4-carbonitrile for Example 1A and aniline, respectively, in Example 1. MS (ESI(-)) m/e 387 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.03 (s, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.63 (d, 1H), 7.48-7.35 (m, 2H), 2.87 (t, 2H), 2.33 (t, 2H), 1.69-1.52 (m, 4H), 1.43-1.23 (m, 2H); Anal. Calcd for $C_{21}H_{19}N_2O_2F_3 \cdot 0.25H_2O$: C, 64.20; H, 5.0; N, 7.13. Found: C, 64.26; H, 5.08; N, 7.13.

Example 58

N-(3-cyanophenyl)-8,8,8-trifluoro-7-oxooctanamide

The desired product was prepared by substituting methyl 8,8,8-trifluoro-7-oxooctanoate and 3-cyanoaniline for Example 1A and aniline, respectively, in Example 1. MS (ESI(-)) m/e 311 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.10 (s, 1H), 7.78 (dd, 1H), 7.56-7.43 (m, 2H), 2.88 (t, 2H), 2.33 (t, 2H), 1.68-1.53 (m, 2H), 1.51-1.20 (m, 4H); Anal. Calcd for $C_{15}H_{15}N_2O_2F_3 \cdot 0.65H_2O$: C, 55.61; H, 5.07; N, 8.65. Found: C, 55.67; H, 5.0; N, 8.51.

Example 59

8,8,8-trifluoro-7-oxo-N-(4-phenoxyphenyl)octanamide

The desired product was prepared by substituting methyl 8,8,8-trifluoro-7-oxooctanoate and 4-phenoxyaniline for Example 1A and aniline, respectively, in Example 1. MS (ESI(-)) m/e 378 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.60 (d, 2H), 7.36 (t, 2H), 7.08 (t, 1H), 6.97 (t, 4H), 2.88 (t, 2H), 2.28 (t, 2H), 1.67-1.52 (m, 4H), 1.41-1.28 (m, 2H); Anal. Calcd for $C_{20}H_{20}NO_3F_3$: C, 63.32; H, 5.31; N, 3.69. Found: C, 63.14; H, 5.22; N, 3.53.

Example 60

N-(4-aminobenzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-(aminomethyl)aniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 329 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.06 (t, 1H), 7.22 (dt, 1H), 7.12 (d, 1H), 7.00 (d, 1H), 6.88 (t, 1H), 4.20 (d, 2H), 2.14 (t, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.42 (m, 2H), 1.22 (m, 4H).

Example 61

9,9,9-trifluoro-N-(3-methylphenyl)-8-oxononanamide

The desired product was prepared by substituting 3-methylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 314 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.44 (s, 1H), 7.36 (d, 1H), 7.15 (t, 1H), 6.85 (d, 1H), 2.28 (t, 2H), 2.26 (s, 3H), 1.6 (m, 4H), 1.44 (m, 2H), 1.28 (m, 4H).

Example 62

9,9,9-trifluoro-N-(4-methylphenyl)-8-oxononanamide

The desired product is prepared by substituting 4-methylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 314 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.42 (d, 2H), 7.04 (d, 2H), 2.28 (t, 2H), 2.26 (s, 3H), 1.62 (m, 4H), 1.22 (m, 6H).

Example 63

N-(4-aminophenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 1,4-benzenediamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 315 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.45 (d, 2H), 7.0 (d, 2H), 6.60 (br s, 2H), 2.24 (t, 2H), 1.46 (m, 4H), 1.40 (m, 2H), 1.22 (m, 4H).

Example 64

9,9,9-trifluoro-N-(4-fluorobenzyl)-8-oxononanamide

The desired product was prepared by substituting (4-fluorophenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 332 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.02 (t, 0.54H), 8.24 (t, 0.46H), 8.00 (m, 1H), 7.35 (m, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 4.42 (d, 1.08H), 4.21 (d, 0.96H), 2.10 (dt, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.42 (m, 2H), 1.24 (m, 4H).

Example 65

9,9,9-trifluoro-N-(3-methoxybenzyl)-8-oxononanamide

The desired product was prepared by substituting (3-methoxyphenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 344 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.00 (t, 1H), 7.22 (t, 1H), 7.05 (dd, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 4.40 (d, 2H), 3.82 (s, 3H), 2.24 (t, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.42 (m, 2H), 1.24 (m, 4H).

Example 66

9,9,9-trifluoro-N-(4-methoxybenzyl)-8-oxononanamide

The desired product was prepared by substituting (4-methoxyphenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 344 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (t, 1H), 7.40 (d, 1H), 7.10 (d, 1H), 7.00 (d, 1H), 6.80 (d, 1H), 4.20 (d, 2H), 3.70 (s, 3H), 2.10 (t, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H), 1.24 (m, 4H).

Example 67

9,9,9-trifluoro-N-(3-fluorobenzyl)-8-oxononanamide

The desired product was prepared by substituting (3-fluorophenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 332 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.20 (t, 0.5H), 8.30 (t, 0.5H), 7.78 (dd, 0.5H), 7.65 (dd, 0.5H), 7.54 (m, 1H), 7.36 (m, 1H), 7.15 (m, 0.5H), 7.05 (m, 0.5H), 4.45 (d, 1H), 4.22 (d, 1H), 2.30 (t, 1H), 2.14 (t, 1H), 1.60 (m, 2H), 1.52 (m, 2H), 1.42 (m, 2H), 1.24 (m, 4H).

Example 68

9,9,9-trifluoro-N-(3-chlorobenzyl)-8-oxononanamide

The desired product was prepared by substituting (3-chlorophenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 348 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.30 (t, 1H), 7.34 (m, 1H), 7.28 (m, 2H), 7.20 (d, 1H), 4.20 (d, 2H), 2.16 (t, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H), 1.22 (m, 4H).

Example 69

N-(4-bromobenzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (4-bromophenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 392 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.30 (t, 1H), 7.50 (d, 2H), 7.20 (d, 2H), 4.20 (d, 2H), 2.12 (m, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H), 1.22 (m, 4H).

Example 70

N-(3-(dimethylamino)phenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting N,N-dimethyl-1,3-benzenediamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 343 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.60 (d, 1H), 7.05 (m, 2H), 6.90 (m, 1H), 6.41 (d, 1H), 2.50 (s, 6H), 2.20 (m, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H), 1.22 (m, 4H).

Example 71

9,9,9-trifluoro-8-oxo-N-(3-(trifluoromethoxy)benzyl)nonanamide

The desired product was prepared by substituting (3-(trifluoromethoxy)phenyl)-methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 398 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.38 (t, 1H), 7.40 (t, 1H), 7.25 (d, 1H), 7.20 (m, 2H), 4.25 (d, 2H), 2.10 (t, 2H), 1.60 (m, 1H), 1.48 (m, 4H), 1.40 (m, 1H), 1.22 (m, 4H).

Example 72

9,9,9-trifluoro-8-oxo-N-(3-(trifluoromethyl)benzyl)nonanamide

The desired product was prepared by substituting (3-(trifluoromethyl)phenyl)-methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 382 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (t, 1H), 7.60 (m, 4H), 4.36 (d, 2H), 2.14 (m, 2H), 1.60 (m, 4H), 1.40 (m, 1H), 1.22 (m, 4H).

Example 73

9,9,9-trifluoro-8-oxo-N-(3-(trifluoromethoxy)phenyl)nonanamide

The desired product was prepared by substituting 3-(trifluoromethoxy)aniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 384 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.52 (d, 1H), 7.40 (m, 2H), 7.0 (d, 1H), 2.30 (m, 2H), 1.60 (m, 5H), 1.40 (m, 1H), 1.20 (m, 4H).

Example 74

N-(3,5-dimethoxybenzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (3,5-dimethoxyphenyl)-methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 374 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 6.56 (s, 1H), 6.40 (s, 2H), 4.20 (d, 2H), 3.60 (s, 6H), 2.12 (t, 2H), 1.60 (m, 1H), 1.54 (m, 4H), 1.40 (m, 1H), 1.22 (m, 4H).

Example 75

N-(2,4-dimethylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 2,4-dimethylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 328 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.20 (d, 1H), 7.00 (s, 1H), 6.95 (d, 1H), 2.24 (t, 2H), 2.20 (s, 3H), 2.14 (s, 3H), 1.60-1.40 (m, 6H), 1.28-1.20 (m, 4H).

Example 76

N-(3,4-dimethylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3,4-dimethylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 328 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.40 (s, 1H), 7.34 (d, 1H), 7.0 (d, 1H), 2.24 (t, 2H), 2.18 (s, 3H), 2.12 (s, 3H), 1.60 (m, 5H), 1.40 (m, 1H), 1.28 (m, 4H).

Example 77

N-(3,5-dimethylphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3,5-dimethylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 328 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.20 (s, 2H), 6.64 (s, 1H), 2.24 (t, 2H), 2.20 (s, 6H), 1.60 (m, 5H), 1.40 (m, 1H), 1.26 (m, 4H).

Example 78

N-(2,4-dimethoxyphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 2,4-dimethoxyaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 360 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6)

δ 8.82 (s, 1H), 7.60 (d, 1H), 6.60 (s, 1H), 6.42 (d, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 2.30 (t, 2H), 1.60 (m, 5H), 1.40 (m, 1H), 1.26 (m, 4H).

Example 79

N-(2,5-dimethoxybenzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (2,5-dimethoxyphenyl)methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 374 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (t, 1H), 6.90 (d, 1H), 6.68 (d, 1H), 6.62 (s, 1H), 4.2 (d, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 2.10 (t, 2H), 1.60-1.40 (m, 6H), 1.20 (m, 4H).

Example 80

N-(3,5-dimethoxyphenyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 3,5-dimethoxyaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 360 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 6.80 (s, 2H), 6.20 (s, 1H), 3.70 (s, 6H), 2.24 (t, 2H), 1.60 (m, 4H), 1.40 (m, 2H), 1.22 (m, 4H).

Example 81

N-(1,3-benzodioxol-5-ylmethyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 1,3-benzodioxol-5-ylmethanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 358 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.80 (t, 1H), 6.86 (d, 1H), 6.82 (s, 1H), 6.76 (d, 1H), 6.0 (s, 2H), 4.20 (d, 2H), 2.10 (t, 2H), 1.80-1.40 (m, 6H), 1.20 (m, 4H).

Example 82

9,9,9-trifluoro-8-oxo-N-(3,4,5-trimethoxyphenyl)nonanamide

The desired product was prepared by substituting 3,4,5-trimethoxyaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 390 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.00 (s, 2H), 3.80 (s, 6H), 3.60 (s, 3H), 2.22 (t, 2H), 1.60 (m, 4H), 1.20 (m, 2H), 1.20 (m, 4H).

Example 83

N-(3,4-dichlorobenzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting (3,4-dichlorophenyl)-methanamine for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 382 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (t, 1H), 7.60 (d, 1H), 7.42 (s, 1H), 7.20 (d, 1H), 4.22 (d, 2H), 2.12 (t, 2H), 1.62-1.40 (m, 6H), 1.20 (m, 4H).

Example 84

8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-3-octyn-2-one

Example 84A

4-(5-hexynyloxy)-1,1'-biphenyl

A solution of (1,1'-biphenyl)-4-ol (1.70 g, 10.0 mmol), 5-hexyn-1-ol (0.98 g, 10.0 mmol), and triphenylphosphine (3.41 g, 13.0 mmol) in THF (20 mL) at 0 °C was treated dropwise with diethylazodicarboxylate (2.27 g, 13.0 mmol), warmed to room temperature, stirred for 18 hours, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 50:1 hexanes/ethyl acetate to provide 1.68 g (67%) of the desired product.

Example 84B

8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-3-octyn-2-one

A solution of Example 84A (1.51 g, 6.0 mmol) in THF (35 mL) at -78 °C was treated dropwise with 2.5 M n-butyllithium in hexanes (2.6 mL, 6.5 mmol) and ethyl trifluoroacetate (0.98 g, 6.9 mmol), stirred for 10 minutes, treated with boron trifluoride diethyl etherate (1.50 g, 10 mmol), stirred for 4 hours, warmed to room temperature, and stirred for 18 hours. The mixture was quenched with saturated NH_4Cl (20 mL), and extracted with diethyl ether. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 95:5 to 92:8 hexanes/ethyl acetate to provide 959 mg (46%) of the desired product. MS (ESI(-)) m/e 345 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62-7.57 (m, 4H), 7.45-7.40 (m, 2H), 7.33-7.27 (m, 1H), 7.02 (d, 2H), 4.06 (t, 2H), 2.78 (t, 2H), 1.91-1.71 (m, 4H); Anal. Calcd for $C_{20}H_{17}F_3O_2$: C, 69.36; H, 4.95. Found: C, 69.45; H, 5.08.

Example 85

N-(4-(dimethylamino)benzyl)-9,9,9-trifluoro-8-oxononanamide

The desired product was prepared by substituting 4-(aminomethyl)-N,N-dimethylaniline for 4-aminopyridine in Example 6. MS (ESI(-)) m/e 357 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.06 (t, 1H), 7.12 (d, 2H), 6.88 (d, 2H), 4.20 (d, 2H), 2.80 (s, 6H), 2.14 (t, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.42 (m, 2H), 1.22 (m, 4H).

Example 86

(3E)-8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-3-octen-2-one

Example 86A

(3E)-8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-3-octen-2-ol

A suspension of LAH (201 mg, 5.3 mmol) in THF (10 mL) at 0 °C was treated dropwise with a solution of Example 84B (822 mg, 2.40 mmol) in THF (2.5 mL), stirred for 30 minutes, warmed to room temperature, heated to reflux for 8 hours, cooled to 0 °C, and treated sequentially with water (0.1 mL), 1M NaOH (0.1 mL), and water (0.5 mL). The suspension was filtered and the filtrate was washed sequentially with saturated NH_4Cl, water, and brine, dried ($MgSO_4$), filtered, and concentrated to provide 660 mg (78%) of the desired product. MS (ESI(+)) m/e 368 $(M+NH_4)^+$.

Example 86B

(3E)-8-((1,1'-biphenyl)-4-yloxy)-1,1,1-trifluoro-3-octen-2-one

A solution of Example 86A (201 mg, 0.57 mmol) in dichloromethane (3 mL) at room temperature was added dropwise to a suspension of Dess-Martin reagent (894 mg, 2.10 mmol) in dichloromethane (20 mL), stirred for 3 hours, diluted with 1M NaOH (20 mL) and diethyl ether (20 mL), and stirred for 30 minutes. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 180 mg (90%) of the desired product. MS (ESI(-)) m/e 347 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62-7.53 (m, 4H), 7.45-7.27 (m, 4H), 7.01 (d, 2H), 6.67 (dd, 1H), 4.03 (t, 2H), 2.49-2.43 (m, 2H), 1.82-1.61 (m, 4H); Anal. Calcd for $C_{20}H_{19}F_3O_2$: C, 68.96; H, 5.50. Found: C, 69.11; H, 5.42.

Example 87

(8E)-9-(1,1'-biphenyl)-4-yl-1,1,1-trifluoro-8-nonen-2-one

Example 87A

ethyl (7E)-8-(1,1'-biphenyl)-4-yl-7-octenoate

A solution of (7-ethoxy-7-oxoheptyl)(triphenyl)phosphonium bromide (599 mg, 1.2 mmol) in THF (5mL) at 0 °C was treated with potassium tert-butoxide (115 mg, 1.2 mmol) and 4-phenylbenzaldehyde (182 mg, 1.0 mmol), stirred for 1.5 hours, warmed to room temperature, and treated with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 5% ethyl acetate/hexanes to provide 244mg (76%) of the desired product. MS (ESI(+)) m/e 323 $(M+H)^+$.

Example 87B

(8E)-9-(1,1'-biphenyl)-4-yl-1,1,1-trifluoro-8-nonen-2-one

The desired product was prepared by substituting Example 87A for Example 2A in Examples 2B and 2C. MS (ESI(-)) m/e 345 $(M-H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.80-7.30 (m, 9H), 6.45 (br d, 1H), 5.69 (dt, 1H), 2.87 (t, 2H), 2.35 (dq, 2H), 1.60-1.50 (m, 2H), 1.50-1.40 (m, 2H), 1.40-1.30 (m, 2H); Anal. Calcd for $C_{21}H_{21}F_3O \cdot 0.7H_2O$: C, 70.61; H, 6.26. Found: C, 70.53; H, 5.76.

Example 88

1-(2-(4-((1,1'-biphenyl)-4-yloxy)butyl)cyclopropyl)-2,2,2-trifluoroethanone

Example 88A

1-(2-(4-((1,1'-biphenyl)-4-yloxy)butyl)cyclopropyl)-2,2,2-trifluoroethanol

Samarium (362 mg, 2.4 mmol) was dried under vacuum with heating, purged with nitrogen, treated with THF (3 mL) and a solution of Example 87A (200 mg, 0.57 mmol) in THF (4 mL), cooled to 0 °C, and treated with CH_2I_2 (0.18 mL, 2.2 mmol). The reaction was warmed to room temperature, stirred for 24 hours, and partitioned between saturated K_2CO_3 and diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by HPLC with 20% ethyl acetate/hexanes to provide 130 mg (63%) of the desired product. MS (APCI(+)) m/e 382 $(M+NH_4)^+$.

Example 88B

1-(2-(4-((1,1'-biphenyl)-4-yloxy)butyl)cyclopropyl)-2,2,2-trifluoroethanone

The desired product was prepared by substituting Example 88A for Example 86A in Example 86B. MS (ESI(+)) m/e 380 $(M+NH_4)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.45-7.39 (m, 2H), 7.33-7.27 (m, 1H), 7.00 (d, 2H), 4.01 (t, 2H), 2.36-2.31 (m, 1H), 1.77-1.71 (m, 2H), 1.70-1.62 (m, 1H), 1.59-1.40 (m, 5H), 1.33-1.27 (m, 1H); Anal. Calcd for $C_{21}H_{21}F_3O_2 \cdot 0.3H_2O$: C, 68.58; H, 5.92. Found: C, 68.37; H, 5.62.

Example 89

9H-fluoren-9-ylmethyl 7,7,7-trifluoro-6-oxoheptylcarbamate

A suspension of Fmoc-ε-aminocaproic acid (4.97g, 14.1 mmol) in dichloromethane (25 mL) at room temperature was treated with oxalyl chloride (2.2 mL, 25.2 mmol), stirred for 1 hour, and concentrated. The concentrate was dissolved in dichloromethane (100 mL), treated with trifluoroacetic anhydride (8.92g, 42.4 mmol), cooled to -50 °C, and treated dropwise with pyridine (5.7 mL, 70 mmol) over 5 minutes. The mixture was warmed to -25 °C, stirred for 1 hour, warmed to 10 °C over 1 hour, cooled to -30 °C, quenched with water (10 mL), and partitioned between dichloromethane and water. The organic phase was

washed with water, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 30% ethyl acetate/hexanes to 50% ethyl acetate/hexanes to 80% ethyl acetate/hexanes to provide 900 mg (16%) of the desired product. mp: 83-88 °C; MS (ESI(+)) m/e 406 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39-1.27 (m, 2H), 1.56-1.43 (m, 2H), 1.63-1.58 (m, 2H), 2.68 (t, 2H), 3.09-2.92 (m, ~0.5H), 3.17 (q, 2H), 4.20 (t, 1H), 4.40 (d, 2H), 4.54-4.43 (m, ~0.5H), 4.89-4.76 (m, 1H), 7.28 (td, 2H), 7.37 (t, 2H), 7.57 (d, 2H), 7.73 (d, 2H); Anal. Calcd for $C_{22}H_{22}F_3NO_3$: C, 65.18; H, 5.47; N, 3.45; F, 14.06. Found: C,64.94; H, 5.53; N, 3.46; F, 13.75.

Example 90

4-((1,1'-biphenyl)-4-yloxy)-N-(3,3,3-trifluoro-2-oxopropyl)butanamide

Example 90A

methyl 4-((1,1'-biphenyl)-4-yloxy)butanoate

A mixture of (1,1'-biphenyl)-4-ol (2.0 g, 11.75 mmol), methyl 4-bromobutyrate (1.55 mL, 12.0 mmol) and Cs_2CO_3 (4.21 g, 12.9 mmol) in DMF (40 mL) at room temperature was stirred for 18 hours, diluted with water (500 mL), and filtered to provide 2.98 g (94%) of the desired product. MS (ESI(+)) m/e 271 $(M+H)^+$.

Example 90B

lithium 4-((1,1'-biphenyl)-4-yloxy)butanoate

A mixture of Example 90A (2.0 g, 8.0 mmol), 2M LiOH in water (24 mL, 48 mmol) and THF (18 mL) at room temperature was stirred for 18 hours, partially concentrated, and filtered. The solid was washed with water and dried in a vacuum oven to provide 1.94 g (93%) of the desired product. MS (ESI(-)) m/e 255 $(M-Li)^-$.

Example 90C

4-((1,1'-biphenyl)-4-yloxy)-N-(3,3,3-trifluoro-2-hydroxypropyl)butanamide

A mixture of Example 90B (206 mg, 0.8 mmol), 2-hydroxy-2-(trifluoromethyl)ethylamine (102 mg, 0.79 mmol, prepared as described in J.Org.Chem. **1995**, 60, 41), EDCI (162 mg, 0.85 mmol), HOBt (115 mg, 0.85 mmol) and NMM (0.17 mL, 1.5 mmol) in DMF (2 mL) at room temperature was stirred for 18 hours, and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to 40% ethyl acetate/hexanes to provide 0.16 g (55%) of the desired product. MS (ESI(-)) m/e 366 $(M-H)^-$.

Example 90D

4-((1,1'-biphenyl)-4-yloxy)-N-(3,3,3-trifluoro-2-oxopropyl)butanamide

The desired product was prepared by substituting Example 90C for Example 86A in Example 86B. MS (ESI(+)) m/e 366 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.08-8.04 (m, 1H), 7.62-7.57 (m, 4H), 7.45-7.40 (m, 2H), 7.32-7.27 (m, 1H), 7.00 (d, 2H), 4.01 (t, 2H), 3.40 (d, 2H), 2.34 (t, 2H), 1.99-1.93 (m, 2H); Anal. Calcd for $C_{19}H_{18}F_3NO_3 \cdot 0.8H_2O$: C, 60.09; H, 5.20; N, 3.69. Found: C, 59.74; H, 5.35; N, 3.51.

Example 91

methyl 8-((1,1'-biphenyl)-4-yloxy)-2-oxooctanoate

Example 91A

6-((4'-phenyl)phenoxy))-hexan-1-ol

A solution of (1,1'-biphenyl)-4-ol (2.3 g, 13.5 mmol) in DMF (15 mL) at room temperature was treated with Cs_2CO_3 (8.8 g, 27 mmol), stirred for 20 minutes, treated with a solution of 6-(t-butyldimethylsilyloxy)hexyl bromide (4.78 g, 16.2 mmol) in DMF (5 mL), stirred for 48 hours, and partitioned between water and diethyl ether. The aqueous phase was extracted with diethyl ether, and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was dissolved in THF (60 mL), treated with 1M TBAF in THF (27 mL, 27 mmol), stirred for 18 hours, poured into water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was triturated with hexanes and filtered to provide the desired product.

Example 91B

6-((1,1'-biphenyl)-4-yloxy)hexanal

A solution of oxalyl chloride (1.24 mL, 14.22 mmol) in dichloromethane (10 mL) at -60 °C was treated dropwise with a solution of DMSO (1.85 mL, 26.1 mmol) in dichloromethane (2 mL), stirred for 10 minutes, treated with a solution of Example 91A (3.2 g, 11.85 mmol) in dichloromethane (10 mL), stirred for 15 minutes, treated with triethylamine (8.19 mL, 59.2 mmol), stirred for 5 minutes, warmed to room temperature, and partitioned between water and dichloromethane. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 10% ethyl acetate/hexanes to provide the desired product.

Example 91C

methyl 8-((1,1'-biphenyl)-4-yloxy)-2-oxooctanoate

A suspension of lithium chloride (24 mg, 0.58 mmol) in acetonitrile (2 mL) at room temperature was treated with a solution of methyl (dimethoxyphosphoryl)-(tetrahydro-2H-pyran-2-yloxy)acetate (150 mg, 0.53 mmol, prepared according to the procedure described in Tet. Lett. **1981**, 22, 663-666) in acetonitrile (1.5 mL), treated with DBU (0.07 mL, 0.47 mmol), stirred for 10 minutes, cooled to 0 °C, treated with a solution of Example 91B (118 mg, 0.44 mmol) in acetonitrile (2 mL), stirred for 1.5 hours, and warmed to room temperature. The reaction was partitioned between water and diethyl ether and the organic extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was dissolved in methanol (10 mL), treated with $pTsOH \cdot H_2O$ (15 mg), stirred for 45 minutes, and concentrated. The concentrate was dissolved in dichloromethane, washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 10% ethyl acetate/hexanes to provide 63 mg (42%) of the desired product. MS (ESI(+)) m/e 358 $(M+NH_4)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.45-7.40 (m, 2H), 7.33-7.28 (m, 1H), 7.01 (d, 2H), 4.00 (t, 2H), 3.32 (s, 3H), 2.83 (t, 2H), 1.77-1.69 (m, 2H), 1.58-1.49 (m, 2H), 1.48-1.32 (m, 4H); Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.07; H, 6.93.

Example 92

7-((1,1'-biphenyl)-3-yloxy)-1-(1,3-oxazol-2-yl)-1-heptanone

Example 92A

ethyl 7-((1,1'-biphenyl)-3-yloxy)heptanoate

The desired product was prepared by substituting (1,1'-biphenyl)-3-ol for (1,1'-biphenyl)-4-ol in Example 2A.

Example 92B

7-((1,1'-biphenyl)-3-yloxy)heptanoic acid

The desired product was prepared by substituting Example 92A for Example 1A in Example 1B.

Example 92C

7-((1,1'-biphenyl)-3-yloxy)heptanoyl chloride

The desired product was prepared by substituting Example 92B for Example 102B in Example 102C.

Example 92D

7-((1,1'-biphenyl)-3-yloxy)-1-(1,3-oxazol-2-yl)-1-heptanone

A solution of oxazole (39 mg, 0.56 mmol) in THF (6 mL) at -78 °C was treated dropwise with 2.5M n-butyllithium in hexanes (0.34 mL, 0.85 mmol), stirred for 20 minutes, treated with 0.5M $ZnCl_2$ in THF (2.26 mL, 1.13 mmol), warmed to 0 °C, and stirred for 45 minutes. The mixture was treated with CuI (107 mg, 0.56 mmol), stirred for 10 minutes, treated dropwise with a solution of Example 92C (1.13 mmol) in THF (4 mL), and stirred for 1 hour. The mixture was treated with ethyl acetate (30 mL), washed sequentially with 15% NH_4OH (20 mL), water (20 mL), and saturated NH_4Cl (10 mL), dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 20 % ethyl acetate/hexanes to provide the desired product. MS (ESI(+)) m/e 350 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.60 (m, 1H), 7.58 (m, 1H), 7.42 (m, 2H), 7.36 (m, 1H), 7.34 (m, 1H), 7.32 (s, 1H), 7.16 (m, 1H), 7.10 (t, 1H), 6.88 (dd, 1H), 4.00 (t, 2H), 3.10 (t, 2H), 1.85-1.75 (m, 4H), 1.55-1.45 (m, 4H).

Example 93

8-((1,1'-biphenyl)-4-yloxy)-2-oxooctanoic acid

The desired product was prepared by substituting Example 91C for Example 1A in Example 1B. MS (ESI(+)) m/e 344 $(M+NH_4)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.45-7.40 (m, 2H), 7.32-7.27 (m, 1H), 7.03-7.00 (m, 2H), 4.00 (t, 2H), 2.66 (t, 2H), 1.77-1.67 (m, 2H), 1.56-1.24 (m, 6H); Anal. Calcd. for $C_{20}H_{22}O_4 \cdot H_2O$: C, 69.75; H, 7.02. Found: C, 69.76; H, 6.70.

Example 94

ethyl 7-((1,1'-biphenyl)-4-yloxy)-2-oxoheptanoate

Example 94A

ethyl 7-((1,1'-biphenyl)-4-yloxy)-2-hydroxyheptanoate

A solution of 0.5M KHMDS in THF (9.2 mL, 4.6 mmol) in THF (100 mL) at -78 °C was treated with a solution of Example 2A (1.0 g, 3.0 mmol) in THF (50 mL), stirred for 15 minutes, treated with 2-benzenesulfonyl-3-phenyl-oxaziridine (1.2 g, 4.6 mmol, prepared according to the procedure described in J. Org. Chem. **1982**, 47, 1774-1775) stirred for 30 minutes, quenched with saturated NH_4Cl, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 4:1 ethyl acetate/dichloromethane to provide 0.51 g (50%) of the desired product.

Example 94B

ethyl 7-((1,1'-biphenyl)-4-yloxy)-2-oxoheptanoate

A solution of Example 94A (155 mg, 0.45 mmol) in dichloromethane (3 mL) at 0 °C was treated sequentially with 4A molecular sieves and PDC (256 mg, 0.68 mmol), warmed to room temperature, stirred for 72 hours, diluted with ethyl acetate, filtered through diatomaceous earth (Celite®), and concentrated. The concentrate was purified by flash column chromatography on silica gel with 8:1 ethyl acetate/hexanes to provide the desired product. MS (DCI/NH_3) m/e 358 $(M+NH_4)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56-7.49 (m, 4H), 7.44-7.38 (m, 2H), 7.32-7.27 (m, 1H), 6.98-6.93 (m, 2H), 4.32 (q, 2H), 4.00 (t, 2H), 2.89 (t, 2H), 1.88-1.69 (m, 4H), 1.60-1.55 (m, 2H), 1.37 (t, 3H); Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.10; H, 7.03.

Example 95

ethyl 7-((3-bromo(1,1'-biphenyl)-4-yl)oxy)-2-oxoheptanoate

Example 95A

4-((5-bromopentyl)oxy)-1,1'-biphenyl

A solution of 1,5-dibromopentane (6.4 mL, 50 mmol) and (1,1'-biphenyl)-4-ol (2.67 g, 15.7 mmol) in DMF (50 mL) at room temperature was treated with Cs_2CO_3 (5.13 g, 15.7 mmol), stirred for 16 hours, poured into water, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 98:2 hexanes/ethyl acetate to provide 2.4 g (48%) of the desired product.

Example 95B

ethyl 2-(5-((1,1'-biphenyl)-4-yloxy)pentyl)-1,3-dithiane-2-carboxylate

A suspension of NaH (224 mg, 8.9 mmol) in toluene (7 mL) at 0 °C was treated sequentially with ethyl-2-dithiane carboxylate (1.03 mL, 6.53 mmol) and a solution of Example 95A (2.3 g, 7.2 mmol) in DMF (2 mL), warmed to room temperature, stirred for 16 hours, poured into water, and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 98:2 hexanes/ethyl acetate to provide 0.52g (19%) of the desired product.

Example 95C

ethyl 7-((3-bromo(1,1'-biphenyl)-4-yl)oxy)-2-oxoheptanoate

A solution of NBS (1.92g, 10.8 mmol) in a 97:3 mixture of acetone/water (19 mL) at 0 °C was treated dropwise with a solution of Example 95B (0.52g, 1.2 mmol) in a 97:3 mixture of acetone/water (3 mL), stirred for 15 minutes, and partitioned between

dichloromethane and 10% Na_2SO_3. The organic phase was washed sequentially with 10% Na_2SO_3, water, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with dichloromethane to provide 0.326g (65%) of the desired product. MS (ESI(+)) m/e 419 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, 1H), 7.65-7.61 (m, 3H), 7.47-7.41 (m, 2H), 7.18 (d, 2H), 4.22 (q, 2H), 4.09 (t, 2H), 2.86 (t, 2H), 1.79-1.77 (m, 2H), 1.63-1.55 (m, 2H), 1.52-1.45 (m, 2H), 1.26 (t, 3H); Anal. Calcd. for $C_{21}H_{23}BrO_4 \cdot 0.5H_2O$: C, 58.89; H, 5.65. Found: C, 58.73; H, 5.37.

Example 96

8-(1,3-oxazol-2-yl)-8-oxo-N-phenyloctanamide

Example 96A

methyl 8-chloro-8-oxooctanoate

The desired product was prepared by substituting 8-methoxy-8-oxooctanoic acid for Example 102B in Example 102C.

Example 96B

methyl 8-(1,3-oxazol-2-yl)-8-oxooctanoate

The desired product was prepared by substituting Example 96A for Example 92C in Example 92D.

Example 96C

8-(1,3-oxazol-2-yl)-8-oxooctanoic acid

The desired product was prepared by substituting Example 96B for Example 1A in Example 1B.

Example 96D

8-(1,3-oxazol-2-yl)-8-oxo-N-phenyloctanamide

The desired product was prepared by substituting Example 96C for Example 1B in Example 1C. MS (ESI(+)) m/e 301 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.40 (s, 1H), 7.60 (d, 2H), 7.50 (s, 1H), 7.32 (t, 2H), 7.00 (t, 1H), 3.00 (t, 2H), 2.28 (t, 2H), 1.60 (m, 4H), 1.32 (m, 4H).

Example 97

N-(1,1'-biphenyl)-3-yl-8-(1,3-oxazol-2-yl)-8-oxooctanamide

The desired product was prepared by substituting Example 96C and (1,1'-biphenyl)-3-

amine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 377 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.40 (s, 1H), 7.90 (s, 1H), 7.60 (dd, 2H), 7.50 (s, 1H), 7.48 (t, 2H), 7.30 (m, 4H), 3.00 (t, 2H), 2.28 (t, 2H), 1.60 (m, 4H), 1.32 (m, 4H).

Example 98

N-(4-chlorophenyl)-8-(1,3-oxazol-2-yl)-8-oxooctanamide

The desired product was prepared by substituting Example 96C and 4-chloroaniline for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 335 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.40 (s, 1H), 7.60 (d, 2H), 7.50 (s, 1H), 7.30 (d, 2H), 3.00 (t, 2H), 2.28 (t, 2H), 1.60 (m, 4H), 1.32 (m, 4H).

Example 99

8-(1,3-oxazol-2-yl)-8-oxo-N-(4-phenoxyphenyl)octanamide

The desired product was prepared by substituting Example 96C and 4-phenoxyaniline for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 393 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.40 (s, 1H), 7.60 (d, 2H), 7.50 (s, 1H), 7.40 (m, 2H), 7.10 (t, 1H), 7.00 (m, 4H), 3.00 (t, 2H), 2.28 (t, 2H), 1.60 (m, 4H), 1.34 (m, 4H).

Example 100

8-(1,3-oxazol-2-yl)-8-oxo-N-(2-pyridinyl)octanamide

The desired product was prepared by substituting Example 96C and 2-aminopyridine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 302 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.40 (s, 1H), 8.30 (m, 1H), 8.00 (d, 1H), 7.80 (m, 1H), 7.50 (s, 1H), 7.10 (m, 1H), 3.00 (t, 2H), 2.32 (t, 2H), 1.60 (m, 4H), 1.34 (m, 4H).

Example 101

8-((1,1'-biphenyl)-4-yloxy)-N-methyl-2-oxooctanamide

Example 101A

mthyl 7-((1,1'-biphenyl)-4-yloxy)heptanoate

The desired product was prepared by substituting methyl 7-bromoheptanoate for ethyl 7-bromoheptanoate in Example 2A.

Example 101B

methyl 7-((1,1'-biphenyl)-4-yloxy)-2-hydroxyheptanoate

The desired product was prepared by substituting Example 101A for Example 2A in Example 94A.

Example 101C

8-((1,1'-biphenyl)-4-yloxy)-2-hydroxy-N-methyloctanamide

A suspension of Example 101B (20 mg, 0.06 mmol) and 2M dimethylamine in methanol (0.3 mL, 0.60 mmol) at room temperature was stirred for 48 hours and concentrated to provide 18 mg of the desired product. MS (ESI(+)) m/e 342 $(M+H)^+$.

Example 101D

8-((1,1'-biphenyl)-4-yloxy)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 101A for Example 86A in Example 86B. MS (ESI(+)) m/e 340 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.45-7.40 (m, 2H), 7.33-7.27 (m, 1H), 7.03-6.98 (m, 2H), 4.00 (t, 2H), 2.82 (t, 2H), 2.64 (d, 3H), 1.77-1.68 (m, 2H), 1.58-1.30 (m, 6H); Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.15; H, 7.60; N, 3.97.

Example 102

1-(1,3-oxazol-2-yl)-7-(phenylsulfanyl)-1-heptanone

Example 102A

ethyl 7-(phenylsulfanyl)heptanoate

The desired product was prepared by substituting thiophenol for (1,1'-biphenyl)-4-ol in Example 2A.

Example 102B

7-(phenylsulfanyl)heptanoic acid

The desired product was prepared by substituting Example 102A for Example 1A in Example 1B.

Example 102C

7-(phenylsulfanyl)heptanoyl chloride

A solution of Example 102B (476 mg, 2 mmol) in dichloromethane at room temperature was treated with oxalyl chloride (0.26 mL, 3 mmol), stirred for 3 hours, and concentrated to provide the desired product.

Example 102D

1-(1,3-oxazol-2-yl)-7-(phenylsulfanyl)-1-heptanone

The desired product was prepared by substituting Example 102C for Example 92C in Example 92D. mp: 39-40 °C; MS (ESI(+)) m/e 290 $(M+H)^+$; ^1H NMR ($CDCl_3$): 7.82 (m,1H), 7.40-7.10 (m, 6H), 3.08 (t, 2H), 2.93 (t, 2H), 1.90-1.30 (m, 8H); Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62, N, 4.61. Found: C, 66.06; H, 6.31; N, 4.61.

Example 103

1-(1,3-oxazol-2-yl)-7-(phenylsulfonyl)-1-heptanone

A solution of Example 102D (230 mg, 0.8 mmol) in 2:1 methanol:water (20 mL) at room temperature was treated with Oxone® (1.22 g, 2 mmol) and $NaHCO_3$ (0.168 g, 2 mmol), stirred for 2 hours, and concentrated. The concentrate was partitioned between water and diethyl ether and the organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide180 mg (70%) of the desired product. mp: 55-56 °C; MS (ESI(+)) m/e 322 $(M+H)^+$; ^1H NMR (DMSO-d_6): 8.39(s, 1H), 8.00-7.60 (m, 5H), 7.52 (s,1H), 3.30 (m, 2H, overlap with H_2O), 2.98 (t, 2H), 1.70-1.20 (m, 8H); Anal. Calcd. for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N 4.36. Found: C, 59.51;, H, 6.13; N, 4.10.

Example 104

7-(2-naphthylsulfanyl)-1-(1,3-oxazol-2-yl)-1-heptanone

Example 104A

ethyl 7-(2-naphthylsulfanyl)heptanoate

The desired product was prepared by substituting 2-naphthalenethiol for (1,1'-biphenyl)-4-ol in Example 2A.

Example 104B

7-(2-naphthylsulfanyl)heptanoic acid

The desired product was prepared by substituting Example 104A for Example 1A in Example 1B.

Example 104C

7-(2-naphthylsulfanyl)heptanoyl chloride

The desired product was prepared by substituting Example 104B for Example 102B in Example 102C.

Example 104D

1-(1,3-oxazol-2-yl)-7-(phenylsulfanyl)-1-heptanone

The desired product was prepared by substituting Example 104C for Example 92C in Example 92D. mp.65-66 °;MS (ESI(+)) m/e 340 $(M+H)^+$; ^{1}H NMR (DMSO-d_6): 8.38 (s, 1H), 7.90-7.70 (m, 4H), 7.55-7.45 (m, 4H), 3.15-2.95 (m, 4H), 1.70-1.30 (m, 8H); Anal. Calcd. for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13. Found: C, 70.78; H, 6.47, N, 3.87.

Example 105

7-(2-naphthylsulfonyl)-1-(1,3-oxazol-2-yl)-1-heptanone

The desired product was prepared by substituting Example 104D for Example 102D in Example 103. mp. 75-76 °C; MS (ESI(+)) m/e 372 $(M+H)^+$; ^{1}H NMR (DMSO-d_6): 8.60-7.50 (m, 9H), 3.35 (m, 2H, overlap with H_2O), 2.98 (t, 2H), 1.65-1.20 (m, 8H); Anal. Calcd. for $C_{20}H_{21}NO_4S$: C, 64.67;H, 5.70;N, 3.77. Found: C, 64.39; H, 5.89; N, 3.53.

Example 106

N-methyl-8-(2-naphthylsulfanyl)-2-oxooctanamide

Example 106A

methyl 8-(2-naphthylsulfanyl)-2-oxooctanoate

The desired product was prepared by substituting 2-naphthalenethiol for 4-phenylphenol in Example 91.

Example 106B

N-methyl-8-(2-naphthylsulfanyl)-2-oxooctanamide

A solution of Example 106A (0.8 g, 2.4 mmol) in THF (5 mL) at room temperature was treated with 2M methylamine in THF (2.4 mL, 4.8 mmol) and triethylamine (7 mL), stirred for 4 hours, and concentrated. Recrystallization from ethyl acetate/hexanes provided 0.55g (69%) of the desired product. mp: 94-95 °C; MS (ESI(-)) m/e 328 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 8.50 (br s, 1H), 7.90-7.30 (m, 7H), 3.07 (t, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.70-1.20 (m, 8H); Anal. Calcd. for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 68.92; H, 6.93; N, 4.05.

Example 107

N-methyl-8-(2-naphthylsulfonyl)-2-oxooctanamide

The desired product was prepared by substituting Example 106B for Example 102D in Example 103. mp. 108-109 °C; MS (ESI(-)) m/e 360 $(M-H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.66 (s, 1H), 8.46 (br s, 1H), 8.30-7.60 (m, 6H), 3.35 (m, 2H, overlap with H_2O), 2.74 (t, 2H), 2.62 (d, 3H), 1.70-1.10 (m,8H); Anal. Calcd. for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N 3.88. Found: C, 62.93; H, 6.26; N, 3.53.

Example 108

8-((1,1'-biphenyl)-4-ylsulfanyl)-N-methyl-2-oxooctanamide

Example 108A

methyl 8-((1,1'-biphenyl)-4-ylsulfanyl)-2-oxooctanoate

The desired product was prepared by substituting (1,1'-biphenyl)-4-thiol for (1,1'-biphenyl)-4-ol in Example 91.

Example 108B

8-((1,1'-biphenyl)-4-ylsulfanyl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 108A for Example 106A in Example 106B. mp: 131-132 °C; MS (ESI(-)) m/e 354 $(M-H)^-$; ^1H NMR (DMSO-d_6) δ 8.50 (br s, 1H), 7.70-7.30 (m, 9H), 3.00 (t, 2H), 2.79 (t, 2H), 2.62 (d, 3H), 1.70-1.20 (m, 8H); Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C 71.05, H 7.13, N, 3.79.

Example 109

8-((1,1'-biphenyl)-4-ylsulfonyl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 108B for Example 102D in Example 103. mp: 134-135 °C; MS (ESI(-)) m/e 388 $(M-H)^-$; ^1H NMR (DMSO-d_6) δ 8.50(br s, 1H), 7.80-7.40 (m, 9H), 3.40 (m, 2H, overlap with H_2O), 2.75 (t, 2H), 2.62(d, 3H), 1.60-1.20 (m, 8H).

Example 110

N-(7-(1,3-oxazol-2-yl)-7-oxoheptyl)-1H-indole-2-carboxamide

Example 110A

methyl 7-((1H-indol-2-ylcarbonyl)amino)heptanoate

The desired product was prepared by substituting methyl 7-aminoheptanoate and 1H-indole-2-carboxylic acid for Example 1B and aniline, respectively, in Example 1C.

Example 110B

7-((1H-indol-2-ylcarbonyl)amino)heptanoic acid

The desired product was prepared by substituting Example 110A for Example 1A in Example 1B.

Example 110C

7-((1H-indol-2-ylcarbonyl)amino)heptanoyl chloride

The desired product was prepared by substituting Example 110B for Example 102B in Example 102C.

Example 110D

N-(7-(1,3-oxazol-2-yl)-7-oxoheptyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 110C for Example 92C in Example 92D. mp: 153-156 °C; MS (ESI(+)) m/e 340 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.40-1.30 (m, 4H), 1.70-1.50 (m, 4H), 3.06-3.01 (t, 2H), 3.34-3.24 (m, 2H), 7.04-6.99 (t, 1H), 7.09-7.08 (d, 1H), 7.18-7.13 (t, 1H), 7.43-7.40 (d, 1H), 7.52 (s, 1H), 7.60-7.58 (d, 1H), 8.38 (s, 1H), 8.44-8.40 (t, 1H), 11.51 (s, 1H); Anal. Calcd. for: $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.98; H, 6.13; N, 12.05.

Example 111

N-(6-(1,3-oxazol-2-yl)-6-oxohexyl)-1H-indole-2-carboxamide

Example 111A

methyl 6-((1H-indol-2-ylcarbonyl)amino)hexanoate

The desired product was prepared by substituting methyl 6-aminohexanoate and 1H-indole-2-carboxylic acid for Example 1B and aniline, respectively, in Example 1C.

Example 111B

6-((1H-indol-2-ylcarbonyl)amino)hexanoic acid

The desired product was prepared by substituting Example 111A for Example 1A in Example 1B.

Example 111C

6-((1H-indol-2-ylcarbonyl)amino)hexanoyl chloride

The desired product was prepared by substituting Example 111B for Example 102B in Example 102C.

Example 111D

N-(6-(1,3-oxazol-2-yl)-6-oxohexyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 111C for Example 92C in Example 92D. mp: 176-179 °C; MS (ESI(+)) m/e 326 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.43-1.35 (m, 2H), 1.73-1.52 (m, 4H), 3.07-3.03 (t, 2H), 7.04-6.99 (t, 1H), 7.08 (s, 1H), 7.19-7.14

(t, 1H), 7.43-7.40 (d, 1H), 7.52 (s, 1H), 7.61-7.58 (d, 1H), 8.38 (s, 1H), 8.44-8.40 (t, 1H), 11.51 (s, 1H); Anal. Calcd. for $C_{18}H_{19}N_3O_3 \cdot 0.25H_2O$: C, 65.54; H, 5.95; N, 12.73. Found: C, 65.63; H, 5.78; N, 12.88.

Example 112

7-((1,1'-biphenyl)-4-yloxy)-1-(4,5-dihydro-1,3-oxazol-2-yl)-1-heptanone

Example 112A

7-(1,1'-biphenyl-4-yloxy)heptan-1-ol

The desired product was prepared by substituting 7-(t-butyldimethylsilyloxy)heptyl bromide for 6-(t-butyldimethylsilyloxy)hexyl bromide in Example 91A.

Example 112B

7-((1,1'-biphenyl)-4-yloxy)heptanal

The desired product was prepared by substituting Example 112A for Example 91A in Example 91B.

Example 112C

8-((1,1'-biphenyl)-4-yloxy)-2-hydroxyoctanenitrile

A mixture of Example 112B (2.0g, 7.1 mmol) and KCN (4.66 g) in THF (25 mL) and water (27 mL) at room temperature was stirred for 2 days and concentrated. The resulting aqueous suspension was filtered to provide the desired product. MS (ESI(+)) m/e 327 $(M+NH_4)^+$.

Example 112D

7-((1,1'-biphenyl)-4-yloxy)-1-(4,5-dihydro-1,3-oxazol-2-yl)-1-heptanol

A solution of acetyl chloride (2.86 mL) in ethanol (2.8 mL) and $CHCl_3$ (5.7 mL) at room temperature was treated with a solution of Example 112C (0.76 g, 2.5 mmol) in $CHCl_3$ (8 mL), stirred overnight, and concentrated. The concentrate was suspended in dichloromethane (12 mL), treated with ethanolamine (0.3 mL) and Et_3N (0.68 mL), stirred for 24 hours, and concentrated. The concentrate was suspended in $CHCl_3$ (50 mL), treated with $TsOH \cdot H_2O$ (46 mg), heated to reflux, and stirred for 3 hours. The reaction was cooled to room temperature, diluted with ethyl acetate, washed sequentially with saturated $NaHCO_3$, water, and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 5% methanol/dichloromethane to provide 0.1 g of the desired product. MS (ESI(+)) m/e 354 $(M+H)^+$.

Example 112E

7-((1,1'-biphenyl)-4-yloxy)-1-(4,5-dihydro-1,3-oxazol-2-yl)-1-heptanone

The desired product was prepared by substituting Example 112D for Example 86A in Example 86B. MS (ESI(+)) m/e 352 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.56-7.49 (m, 4H), 7.43-7.38 (m, 2H), 7.32-7.27 (m, 1H), 6.98-6.93 (m, 2H), 4.42 (t, 2H), 4.08 (t, 2H), 3.99 (t, 2H), 2.94 (t, 2H), 1.85-1.66 (m, 4H), 1.57-1.39 (m, 4H). Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.32; H, 6.98; N, 3.89.

Example 113

9-((1,1'-biphenyl)-4-yloxy)-2,3-nonanedione

Example 113A

4-((5-iodopentyl)oxy)-1,1'-biphenyl

A suspension of 5-((4'-phenyl)phenoxy))-pentan-1-ol (0.85 g, 3.3 mmol) in dichloromethane (20 mL) was treated with methanesulfonyl chloride (0.28 mL, 3.6 mmol) and Et_3N (0.7 mL, 5 mmol), stirred at 0 °C for 1 hour, and partitioned between water and dichloromethane. The organic extract was washed with water, dried (Na_2SO_4), filtered, and concentrated. The concentrate was dissolved in acetone (30 mL), treated with NaI (2.5 g, 16.6 mmol), heated to 70 °C for 18 hours, cooled to room temperature, diluted with water, and extracted three times with ethyl acetate. The combined organic extracts were washed sequentially with aqueous NaS_2O_3, water, and brine, dried ($MgSO_4$), filtered, and concentrated to provide 1.2 g of the desired product. MS (ESI(+)) m/e 384 $(M+NH_4)^+$.

Example 113B

methyl 7-((1,1'-biphenyl)-4-yloxy)-2-(2,2-dimethoxypropanoyl)heptanoate

A solution of NaH (64 mg, 1.6 mmol) in DMF (3 mL) at 0 °C was treated dropwise with methyl 4,4-dimethoxy-3-oxopentanoate (0.29 mL, 1.7 mmol), stirred for 1 hour, treated with a solution of Example 113A (0.5 g, 1.37 mmol) in DMF (4 mL), warmed to room temperature, and stirred for 36 hours. The reaction was quenched with water, and extracted 3 times with ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 15% ethyl acetate/hexanes to provide 0.46 g (79%) of the desired product.

Example 113C

9-((1,1'-biphenyl)-4-yloxy)-2,2-dimethoxy-3-nonanone

A solution of Example 113B (134 mg, 0.31 mmol) in methanol (4 mL) at room temperature was treated with 2N NaOH (0.63 mL), stirred for 3 hours, heated to 70 °C, stirred for 2 hours, cooled to room temperature, diluted with water, and extracted 3 times with ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to provide 92 mg (80%) of the desired product. mp: 48 °C.

Example 113D

9-((1,1'-biphenyl)-4-yloxy)-2,3-nonanedione

A solution of Example 113C (67 mg, 0.18 mmol) in THF (2 mL) and 4N HCl (1 mL) was heated at 40 °C for 1.5h. The reaction was cooled to r.t., diluted with water, extracted 2 times with EtOAc. The combined organic extracts were washed with water, brine, dried (MgSO4), concentrated. The residue was triturated with hexane to give 43 mg (73% yield) of the title compound. mp: 110-111 °C; MS (CI(+)) m/e 342 $(M+NH_4)^+$; ^1H NMR (DMSO-d_6) δ 7.60 (m, 4H), 7.43 (t, 2H), 7.30 (t, 1H), 7.01 (d, 2H), 4.00 (t, 2H), 2.70 (t, 2H), 2.23 (s, 3H), 1.72 (m, 2H), 1.51 (quint, 2H), 1.48-1.30 (m, 4H); Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.52; H, 7.19.

Example 114

N-(1,1'-biphenyl)-4-yl-7,8-dioxononanamide

Example 114A

6-ethyl 1-methyl 2-(2,2-dimethoxypropanoyl)hexanedioate

The desired product was prepared by substituting ethyl 4-bromobutanoate for Example 113A in Example 113B.

Example 114B

ethyl 7,7-dimethoxy-6-oxooctanoate

The desired product was prepared by substituting Example 114A for Example 113B in Example 113C.

Example 114C

N-(1,1'-biphenyl)-4-yl-7,7-dimethoxy-6-oxooctanamide

The desired product was prepared by substituting Example 114B and (1,1'-biphenyl)-4-amine for Example 1B and aniline, respectively, in Example 1C.

Example 114D

N-(1,1'-biphenyl)-4-yl-7,8-dioxononanamide

The desired product was prepared by substituting Example 114C for Example 113C in Example 113D. MS (CI(+)) m/e 355 $(M+NH_4)^+$; ^1H NMR ($CDCl_3$) δ 7.62-7.52 (m, 4H), 7.42 (t, 2H), 7.32 (t, 1H), 7.02 (br s, 1H), 2.77 (t, 2H), 2.39 (t, 2H), 2.33 (s, 3H), 1.77 (quint, 2H), 1.65 (quint, 2H), 1.48-1.36 (m, 2H).

Example 115

methyl 7-((1,1'-biphenyl)-4-yloxy)-2-oxoheptanoate

The desired product was prepared by substituting 5-(t-butyldimethylsilyloxy)pentyl bromide (prepared according to the procedure described in *Can. J. Chem.* **1994**, *72*, 1500-1511) for 6-(t-butyldimethylsilyloxy)hexyl bromide in Example 91. MS (ESI(+)) m/e 327 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 7.62-7.56 (m, 4H), 7.44-7.39 (t, 2H), 7.32-7.27 (m, 1H), 7.00 (d, 2H), 4.00 (t, 2H), 3.77 (s, 3H), 2.86 (t, 2H), 1.78-1.69 (m, 2H), 1.63-1.53 (m, 2H), 1.49-1.40 (m, 2H).

Example 116

methyl 9-((1,1'-biphenyl)-3-ylamino)-2,9-dioxononanoate

Example 116A

N-(1,1'-biphenyl)-3-yl-6-(1,3-dioxolan-2-yl)hexanamide

The desired product was prepared by substituting 6-(1,3-dioxolan-2-yl)hexanoic acid and (1,1'-biphenyl)-3-amine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 340 $(M+H)^+$.

Example 116B

N-(1,1'-biphenyl)-3-yl-7-oxoheptanamide

A solution of Example 116A (2.35g, 6.9 mmol) in acetone (20 mL) and water (2 mL) was treated with $TsOH \cdot H_2O$ (15 mg), heated to reflux, stirred overnight, cooled to room tempearature, and concentrated. The concentrate was dissolved in ethyl acetate, washed with water, dried (Na_2SO_4), filtered, and concentrated to provide 1.82 g (89%) of the desired product. MS (ESI(+)) m/e 296 $(M+H)^+$.

Example 116C

methyl 9-((1,1'-biphenyl)-3-ylamino)-2,9-dioxononanoate

The desired product was prepared by substituting Example 116B for Example 91B in Example 91C. MS (ESI(+)) m/e 368 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.95 (s, 1H), 7.92 (br

s, 1H), 7.62-7.55 (m, 3H), 7.50-7.43 (m, 2H), 7.40-7.28 (m, 3H), 3.76 (s, 3H), 2.82 (t, 2H), 2.32 (t, 2H), 1.64-1.47 (m, 4H), 1.46-1.37 (m, 4H).

Example 117

methyl 9-anilino-2,9-dioxononanoate

Example 117A

6-hydroxy-N-phenylhexanamide

The desired product was prepared by substituting 6-hydroxyhexanoic acid for Example 1B in Example 1C.

Example 117B

methyl 9-anilino-2,9-dioxononanoate

The desired product was prepared by substituting Example 117A for Example 91A in Example 91. MS (ESI(+)) m/e 292 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.82 (s, 1H), 7.57 (d, 2H), 7.27 (t, 2H), 7.01 (t, 1H), 3.76 (s, 3H), 2.81 (t, 2H), 2.28 (t, 2H), 1.62-1.48 (m, 4H), 1.33-1.26 (m, 4H).

Example 118

methyl 8-((4'-cyano(1,1'-biphenyl)-4-yl)oxy)-2-oxooctanoate

The desired product was prepared by substituting 4'-hydroxy(1,1'-biphenyl)-4-carbonitrile for (1,1'-biphenyl)-4-ol in Example 91. MS (ESI(-)) m/e 364 $(M-H)^-$.

Example 119

8-((4'-cyano(1,1'-biphenyl)-4-yl)oxy)-N-methyl-2-oxooctanamide

A suspension of Example 118 (261 mg, 0.7 mmol) and $MeNH_2 \cdot HCl$ (150 mg, 2.2 mmol) in CH_3CN (5 mL) and Et_3N (10 mL) at room temperature was stirred in a sealed vessel for 18 hours, then partitioned between water and ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 30% ethyl acetate/hexanes to provide 113 mg (44%) of the desired product. MS (ESI(-)) m/e 363 $(M-H)^-$; ^1H NMR (DMSO-d_6) δ 8.53-8.48 (m, 1H), 7.90-7.83 (m, 4H), 7.70 (d, 2H), 7.05 (d, 2H), 4.04-4.00 (m, 2H), 2.82 (t, 2H), 2.64 (d, 3H), 1.78-1.68 (m, 2H), 1.58-1.47 (m, 2H), 1.47-1.30 (m, 4H).

Example 120

N^9-(1,1'-biphenyl)-3-yl-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 116 for Example 118 in Example 119. MS (ESI(+)) m/e 367 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.95 (s, 1H), 8.53-8.48 (m, 1H), 7.92-7.90 (m, 1H), 7.61-7.54 (m, 3H), 7.50-7.43 (m, 2H), 7.40-7.28 (m, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.32 (t, 2H), 1.63-1.55 (m, 2H), 1.55-1.47 (m, 2H), 1.34-1.28 (m, 4H).

Example 121

(7E)-8-(1,1'-biphenyl)-4-yl-1-(1,3-oxazol-2-yl)-7-octen-1-one

Example 121A

(7E)-8-(1,1'-biphenyl)-4-yl-7-octenoic acid

The desired product was prepared by substituting Example 87A for Example 1A in Example 1B.

Example 121B

(7E)-8-(1,1'-biphenyl)-4-yl-7-octenoyl chloride

The desired product was prepared by substituting Example 121A for Example 102B in Example 102C.

Example 121D

(7E)-8-(1,1'-biphenyl)-4-yl-1-(1,3-oxazol-2-yl)-7-octen-1-one

The desired product was prepared by substituting Example 121C for Example 92C in Example 92D. MS (ESI(+)) m/e 346 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.39 (s, 1H), 7.70-7.64 (m, 4H), 7.52 (s, 1H), 7.50-7.43 (m, 2H), 7.40-7.32 (m, 3H), 6.44 (br d, 1H), 5.69 (dt, 1H), 3.03 (t, 2H), 2.40-2.31 (m, 2H), 1.69-1.59 (m, 2H), 1.53-1.32 (m, 4H).

Example 122

4-((1E)-8-(1,3-oxazol-2-yl)-8-oxo-1-octenyl)benzonitrile

Example 122A

ethyl (7E)-8-(4-cyanophenyl)-7-octenoate

The desired product was prepared by substituting 4-cyanobenzaldehyde for 4-phenylbenzaldehyde in Example 87A.

Example 122B

(7E)-8-(4-cyanophenyl)-7-octenoic acid

The desired product was prepared by substituting Example 122A for Example 1A in Example 1B.

Example 122C

(7E)-8-(4-cyanophenyl)-7-octenoyl chloride

The desired product was prepared by substituting Example 122B for Example 102B in Example 102C.

Example 122D

4-((1E)-8-(1,3-oxazol-2-yl)-8-oxo-1-octenyl)benzonitrile

The desired product was prepared by substituting Example 122C for Example 92C in Example 92D. MS (ESI(+)) m/e 295 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.38 (s, 1H), 7.80 (d, 2H), 7.53 (s, 1H), 7.46 (d, 2H), 6.48 (br d, 1H), 5.89-5.79 (m, 1H), 3.01 (t, 2H), 2.34-2.27 (m, 2H), 1.67-1.56 (m, 2H), 1.51-1.30 (m, 4H).

Example 123

N^9-(1,1'-biphenyl)-3-yl-2-oxononanediamide

A suspension of Example 116 (354mg, 0.96mmol) in ethanol (5 mL) at room temperature was treated with concentrated NH_4OH (1 mL), stirred for 2 hours, and filtered. The isolated solid was washed with ethanol and dried under vacuum with heating to provide 158 mg (47%) of the desired product. MS (ESI(+)) m/e 353 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.96 (s, 1H), 7.94-7.89 (m, 2H), 7.64-7.54 (m, 4H), 7.50-7.43 (m, 2H), 7.41-7.29 (m, 3H), 2.78 (t, 2H), 2.32 (t, 2H), 1.63-1.54 (m, 2H), 1.54-1.45 (m, 2H), 1.34-1.26 (m, 4H).

Example 124

N^1-methyl-2-oxo-N^9-(4-phenyl-1,3-thiazol-2-yl)nonanediamide

Example 124A

benzyl 7-hydroxyheptanoate

A solution of methyl 6-hydroxyhexanoate (5.0 g, 31.0 mmol, prepared according to the procedure described in Syn.Comm. **1991**, 21 1075) in THF (11 mL) was treated with 2M LiOH (16 mL), heated to 60 °C for 4 hours, heated to 85 °C for 2 hours, and concentrated under nitrogen. The crude product was suspended in DMF (100 mL), treated with $NaHCO_3$(5.26 g, 6.3 mmol) and a solution of benzyl bromide (9.3 mL, 78 mmol) in DMF (50 mL), stirred for 18 hours, poured into water, and exctracted three times with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 10% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to provide 4.43g (60%) of the desired product. MS (ESI(+)) m/e 237 $(M+H)^+$.

Example 124B

benzyl 7-oxoheptanoate

The desired product was prepared by substituting Example 124A for Example 91A in Example 91B.

Example 124C

9-benzyl 1-methyl 2-oxononanedioate

The desired product was prepared by substituting Example 124B for Example 91B in Example 91C.

Example 124D

benzyl 9-(methylamino)-8,9-dioxononanoate

The desired product was prepared by substituting Example 124C for Example 118 in Example 119. MS (ESI(+)) m/e 306 $(M+H)^+$.

Example 124E

9-(methylamino)-8,9-dioxononanoic acid

A solution of Example 124D (0.89 g, 2.91 mmol) and 10% Pd/C (95 mg) in methanol (15 mL) was stirred for 1 hour under a hydrogen atmosphere, filtered through diatomaceous earth (Celite®), and concentrated to provide 0.56g (89 %) of the desired product. MS (ESI(+)) m/e 216 $(M+H)^+$.

Example 124F

N^1-methyl-2-oxo-N^9-(4-phenyl-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-phenyl-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (APCI(+)) m/e 374 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H), 8.53-8.74 (br m, 1H), 7.89 (d, 2H), 7.59 (s, 1H), 7.43 (t, 2H), 7.34-7.29 (m, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.65-1.55 (m, 2H), 1.55-1.45 (m, 2H), 1.32-1.26 (m, 4H).

Example 125

N^1-methyl-2-oxo-N^9-(4-phenoxyphenyl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-phenoxyaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 383 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.87 (s, 1H), 8.52-8.47 (br m, 1H), 7.59

(d, 2H), 7.48-7.43 (m, 2H), 7.11-7.06 (m, 1H), 6.98-7.93 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.28 (t, 2H), 1.62-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 126

N^9-(4,5-diphenyl-1,3-thiazol-2-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4,5-diphenyl-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 450 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.26 (s, 1H), 8.52-8.47 (br m, 1H), 7.44-7.29 (m, 10H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.64-1.56 (m, 2H), 1.54-1.44 (m, 2H), 1.33-1.26 (m, 4H).

Example 127

N^9-(4-(3-methoxyphenyl)-1,3-thiazol-2-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(3-methoxyphenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 404 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.19 (s, 1H), 8.53-8.47 (br m, 1H), 7.62 (s, 1H), 7.49-7.44 (m, 2H), 7.38-7.27 (m, 1H), 6.91-6.84 (m, 1H), 3.80 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.64-1.55 (m, 2H), 1.53-1.43 (m, 2H), 1.32-1.23 (m, 4H).

Example 128

N^9-(4-(2-methoxyphenyl)-1,3-thiazol-2-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2-methoxyphenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 404 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.12 (s, 1H), 8.53-8.47 (br m, 1H), 8.05 (dd, 1H), 7.62 (s, 1H), 7.33-7.37 (m, 1H), 7.14-7.11 (m, 1H), 7.05-7.00 (m, 1H), 3.91 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.64-1.56 (m, 2H), 1.56-1.44 (m, 2H), 1.32-1.25 (m, 4H).

Example 129

N^1-methyl-N^9-(5-methyl-4-phenyl-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 5-methyl-4-phenyl-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 388 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.03 (s, 1H), 8.52-8.47 (br m, 1H), 7.54-7.51 (m, 2H), 7.44 (t, 2H), 7.34-7.31 (m, 1H), 2.79 (t, 2H), 2.64 (d, 3H), 2.46 (s, 3H), 2.41 (t, 2H), 1.62-1.54 (m, 2H), 1.54-1.44 (m, 2H), 1.30-1.25 (m, 4H).

Example 130

N^1-methyl-2-oxo-N^9-(4'-(trifluoromethoxy)(1,1'-biphenyl)-3-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(4-trifluoromethoxyphenoxy)aniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 451 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.98 (s, 1H), 8.53-8.48 (br m, 1H), 8.05-8.03 (m, 1H), 7.72 (d, 2H), 7.59-7.56 (m, 1H), 7.48-7.30 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.32 (t, 2H), 1.64-1.55 (m, 2H), 1.55-1.46 (m, 2H), 1.33-1.28 (m, 4H).

Example 131

N^9-(4-(4-chlorophenoxy)phenyl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-chlorophenoxy)aniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 417 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.89 (s, 1H), 8.53-8.46 (br m, 1H), 7.61 (d, 2H), 7.40 (d, 2H), 7.01-6.95 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.28 (t, 2H), 1.62-1.45 (m, 4H), 1.33-1.26 (m, 4H).

Example 132

N^9-(4-methoxy(1,1'-biphenyl)-3-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-methoxy(1,1'-biphenyl)-3-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 397 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.53-8.47 (br m, 1H), 8.30-8.28 (br s, 1H), 7.56 (d, 2H), 7.46-7.41 (m, 2H), 7.38-7.29 (m, 2H), 7.12 (d, 1H), 3.87 (s, 3H), 2.81 (t, 2H), 2.64 (d, 3H), 2.43-2.36 (m, 2H), 1.63-1.48 (m, 4H), 1.34-1.27 (m, 4H).

Example 133

N^9-(4'-cyano(1,1'-biphenyl)-3-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 3'-amino(1,1'-biphenyl)-4-carbonitrile for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 392 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H), 8.52-8.47 (br m, 1H), 8.02-8.00 (br m, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.63-7.59 (m, 1H), 7.46-7.38 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.32 (t, 2H), 1.64-1.45 (m, 4H), 1.33-1.28 (m, 4H).

Example 134

N^9-(4-bromophenyl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-bromoaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 368

$(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.97 (s, 1H), 8.52-8.47 (br s, 1H), 7.55 (d, 2H), 7.46 (d, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 2.28 (t, 2H), 1.61-1.44 (m, 4H), 1.32-1.24 (m, 4H).

Example 135

N^9-(6-methoxy(1,1'-biphenyl)-3-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 6-methoxy(1,1'-biphenyl)-3-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 397 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.76 (s, 1H), 8.52-8.47 (br m, 1H), 7.54-7.51 (m, 2H), 7.45-7.36 (m, 4H), 7.34-7.29 (m, 1H), 7.03 (d, 1H), 3.72 (s, 3H), 2.79 (t, 2H), 2.64 (d, 3H), 2.26 (t, 2H), 1.61-1.45 (m, 4H), 1.32-1.25 (m, 4H).

Example 136

N^9-(1,1'-biphenyl)-4-yl-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and (1,1'-biphenyl)-4-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 367 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.94 (s, 1H), 8.52-8.47 (br m, 1H), 7.70-7.58 (m, 6H), 7.44 (t, 2H), 7.32 (t, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.32 (t, 2H), 1.63-1.56 (m, 2H), 1.55-1.46 (m, 2H), 1.33-1.27 (m, 4H).

Example 137

N^9-(3,4-dichlorophenyl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 3,4-dichloroaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 359 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 10.15 (s, 1H), 8.53-8.47 (br s, 1H), 7.99 (d, 1H), 7.54 (d, 1H), 7.47 (dd, 1H), 2.79 (t, 2H), 2.64 (d, 3H), 2.30 (t, 2H), 1.62-1.44 (m, 4H), 1.32-1.25 (m, 4H).

Example 138

N^1-methyl-2-oxo-N^9-(4-(trifluoromethyl)phenyl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-trifluoromethylaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 359 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 10.21 (s, 1H), 8.52-8.47 (br m, 1H), 7.80 (d, 2H), 7.64 (d, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 2.33 (t, 2H), 1.63-1.44 (m, 4H), 1.33-1.26 (m, 4H).

Example 139

N^9-(3-cyanophenyl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 3-cyanoaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 316 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 10.20 (s, 1H), 8.53-8.46 (br m, 1H), 8.10-8.08 (br m, 1H), 7.80-7.76 (m, 1H), 7.51-7.47 (m, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 2.32 (t, 2H), 1.63-1.44 (m, 4H), 1.32-1.26 (m, 4H).

Example 140

N^9-(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-methoxyphenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 404 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.15 (s, 1H), 8.53-8.48 (br m, 1H), 7.81 (d, 2H), 7.42 (s, 1H), 6.98 (d, 2H), 3.79 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.64-1.54 (m, 2H), 1.54-1.44 (m, 4H), 1.31-1.26 (m, 4H).

Example 141

methyl 8-((4'cyano(1,1'-biphenyl)-4-yl)oxy)-3-hydroxy-2oxooctanoate

Example 141A

4'-((6-oxohexyl)oxy)-1,1'-biphenyl-4-carbonitrile

The desired product was prepared by substituting 4'-hydroxy-1,1'-biphenyl-4-carbonitrile for (1,1'-biphenyl)-4-ol in Examples 91A and 91B. MS (ESI(-)) m/e 292 $(M-H)^-$.

Example 141B

methyl (2Z)-2-((tert-butyl(dimethyl)silyl)oxy)-8-((4'-cyano-1,1'-biphenyl-4-yl)oxy)oct-2-enoate

The desired product was prepared by substituting Example 141A for Example 142B in Example 142C. MS (ESI(+)) m/e 480 $(M+H)^+$.

Example 141C

methyl 2-((tert-butyl(dimethyl)silyl)oxy)-3-(5-((4'-cyano-1,1'-biphenyl-4-yl)oxy)pentyl)oxirane-2-carboxylate

A solution of Example 141B (0.68 g, 1.42 mmol) in dichloromethane (10 mL) at room temperature was treated with 70% m-CPBA (350 mg, 1.42 mmol), stirred for 24 hours, treated with activated KF (150 mg), and stirred for 3 hours. The suspension was filtered and the filtrate was concentrated and purified by flash column chromatography on silica gel with 5:1 hexanes/ethyl acetate to provide 0.5 g (71% yield) of the desired product.

Example 141D

methyl 8-((4'cyano(1,1'-biphenyl)-4-yl)oxy)-3-hydroxy-2oxooctanoate

An solution of Example 141C (50 mg, 0.1 mmol) in acetonitrile (1 mL) at 0 °C was treated with $Et_3N{\cdot}HF$ (2 drops), warmed to room temperature, stirred for 24 hours, adjusted to pH 7 with saturated $NaHCO_3$, diluted with water, and filtered. The filter cake was washed with water and dried under vacuum to provide 10 mg (26% yield) of the desired product. MS (DCI) m/e 399 $(M+NH_4)^+$; ^1H NMR (DMSO-d_6) δ 7.89-7.82 (m, 4H), 7.72-7.68 (m, 2H), 7.06-7.03 (m, 2H), 6.84 (d, 1H), 4.22 (d, 1H), 4.00 (t, 2H), 3.70 (s, 3H), 1.74-1.64 (m, 2H), 1.44-1.18 (m, 6H); Anal Calcd for $C_{22}H_{23}NO_5{\cdot}0.25H_2O$: C, 68.47; H, 6.14; N, 3.63. Found: C, 68.63; H, 6.21; N, 3.45.

Example 142

N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-2-carboxamide

Example 142A

tert-butyl 6-hydroxyhexylcarbamate

A solution of 6-aminohexan-1-ol (5.03 g, 42.9 mmol) in THF (35 mL) at room temperature was treated portionwise with $(Boc)_2O$ (8.9 g, 40.1 mmol), stirred for 1 hour, and filtered. The filtrate was concentrated, diluted with diethyl ether, washed sequentially with 1M HCl, water, and brine, dried ($MgSO_4$), and concentrated to provide the desired product (7.83 g). MS (ESI(+)) m/e 218 $(M+H)^+$.

Example 142B

tert-butyl 6-oxohexylcarbamate

A solution of oxalyl chloride (3.64 mL,41.7 mmol) in dichloromethane (200 mL) at -78 °C was treated dropwise with DMSO (6 mL, 84.6 mmol), stirred for 5 minutes, treated with a solution of Example 142A (7.56 g, 34.8 mmol) in dichloromethane(100 mL), stirred for 15 minutes, treated with triethylamine (24 mL, 172 mmol), and warmed to room temperature. The reaction was partitioned between water and dichloromethane and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 10 to 20% ethyl acetate/hexanes to provide 6.44g (86% yield) of the desired product.

Example 142C

methyl (2Z)-8-((tert-butoxycarbonyl)amino)-2-((tert-butyl(dimethyl)silyl)oxy)oct-2-enoate

A suspension of LiCl (1.5 g, 36 mmol)in THF (50 mL) at room temperature was treated with a solution of methyl ((tert-

butyl(dimethyl)silyl)oxy)(dimethoxyphosphoryl)acetate (6.25 g, 20 mmol) in THF (25 mL), treated with DBU (3.6 mL, 24 mmol), stirred for 15 minutes, cooled to 0 °C , treated with a solution of Example 142B (4.3 g, 20 mmol) in THF (25 mL), cooled to 0 °C, stirred for 30 minutes, warmed to room temperature, and stirred for 18 hours. The mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to provide the desired product (7.81 g). MS (ESI(+)) m/e 402 $(M+H)^+$.

Example 142D

methyl 8-((tert-butoxycarbonyl)amino)-2-oxooctanoate

A solution of Example 142C (7.81 g, 19.4 mmol) in acetonitrile (200 mL) at 0 °C was treated with acetic acid (4 mL, 97 mmol) and CsF (5.89 g, 38 mol), stirred at 0 °C for 1 hour, warmed to room temperature, and stirred for 18 hours. The reaction mixture was diluted with 1:1 hexanes/ethyl acetate (400 mL), washed sequentially with $NaHCO_3$ (9.8 g in 200 mL water), water, and brine, dried ($MgSO_4$), filtered, and concentrated to provide 4.43g (79%) of the desired product. MS (ESI(+)) m/e 286 $(M+H)^+$.

Example 142E

tert-butyl 8-(methylamino)-7,8-dioxooctylcarbamate

The desired product was prepared by substituting Example 142D for Example 106A in Example 106B.

Example 142F

8-amino-N-methyl-2-oxooctanamide

Example 142E (1.06 g, 3.9 mmol) at room temperature was treated with 4N HCl in dioxane (10 mL), stirred for 1 hour, and concentrated under a stream of nitrogen to provide 0.809 g of the desired product as the hydrochoride salt. MS (ESI(+)) m/e 187 $(M+H)^+$.

Example 142G

N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 142F and 1H-indole-2-carboxylic acid for aniline and Example 1B, respectively, in Example 1C. MS (ESI(+)) m/e 330 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 11.50 (br s, 1H), 8.53-8.48 (br m, 1H), 8.43-8.39 (br m, 1H), 7.59 (d, 1H), 7.41 (d, 1H), 7.19-7.13 (m, 1H), 7.08 (d, 1H), 7.04-6.99 (m, 1H), 3.29-3.23 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.58-1.47 (m, 4H), 1.37-1.28 (m, 4H).

Example 143

N-(7-(methylamino)-6,7-dioxoheptyl)-1H-indole-2-carboxamide

Example 143A

7-amino-N-methyl-2-oxoheptanamide

The desired product was prepared as the hydrochloride salt by substituting 5-aminohexan-1-ol for 6-aminohexan-1-ol in Examples 142A-142F.

Example 143B

N-(7-(methylamino)-6,7-dioxoheptyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 143A and 1H-indole-2-carboxylic acid for aniline and Example 1B, respectively, in Example 1C. MS (ESI(+)) m/e 316 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 11.51 (s, 1H), 8.52-8.47 (br m, 1H), 8.43-8.39 (br m, 1H), 7.59 (d, 1H), 7.41 (d, 1H), 7.19-7.13 (m, 1H), 7.08 (d, 1H), 7.05-6.99 (m, 1H), 3.31-3.23 (m, 2H), 2.82 (t, 2H), 2.64 (d, 3H), 1.59-1.49 (m, 4H), 1.38-1.28 (m, 2H).

Example 144

N-(7-(methylamino)-6,7-dioxoheptyl)-1,1'-biphenyl-4-carboxamide

Example 143A was coupled with 4-phenylbenzoic acid following the procedures of Example 1C to provide the desired product. MS (ESI(+)) m/e 353 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.52-8.46 (m, 2H), 7.93 (d, 2H), 7.77-7.71 (m, 4H), 7.52-7.47 (m, 2H), 7.43-7.40 (m, 1H), 3.31-3.25 (m, 2H), 2.82 (t, 2H), 2.64 (d, 3H), 1.59-1.49 (m, 4H), 1.37-1.29 (m, 2H).

Example 145

7-(((4-chlorophenyl)sulfonyl)amino)-N-methyl-2-oxoheptanamide

A solution of Example 143A (125 mg, 0.6 mmol) in DMF (3 mL) at room temperature was treated with 4-chlorophenylsulfonyl chloride (127 mg, 0.6 mmol) and Et_3N (0.17 mL,1.2 mmol), stirred for 18 hours, and treated with cold water. The precipitate was collected by filtration and the filter cake was washed with water and dried under vacuum to provide 156 mg (75%) of the desired product. MS (ESI(+)) m/e 347, 349 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.52-8.48 (br m, 1H), 7.79 (d, 2H), 7.68-7.65 (m, 3H), 2.77-2.69 (m, 4H), 2.64 (d, 3H), 1.46-1.31 (m, 4H), 1.25-1.17 (m, 2H).

Example 146

N~1~-methyl-2-oxo-N~9~-phenylnonanediamide

The desired product was prepared by substituting Example 124E and aniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 291 $(M+H)^+$; ^1H NMR (300 mHz, DMSO-d_6) δ 9.82 (s, 1H), 8.53-8.47 (m, 1H), 7.59-7.56 (m,

2H),), 7.29 (t, 2H), 7.04-6.98 (m, 1H), 7.04-6.98 (m, 1H), 2.64 (d, 3H), 2.28 (t, 2H), 1.63-1.45 (m, 4H), 1.32-1.27 (m, 4H).

Example 147

N~1~-methyl-2-oxo-N~9~-(1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 2-aminothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 298 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.53-8.48 (m, 1H), 7.44 (d, 1H), 7.17 (d, 1H), 2.79 (t, 2H), 2.64 (d, 3H), 2.41 (t, 2H), 1.63-1.45 (m, 4H), 1.30-1.24 (m, 4H).

Example 148

N~9~-(4-methoxyphenyl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-methoxyaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 321 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.53-8.46 (m, 1H), 7.47 (d, 2H), 6.85 (d, 2H), 3.71 (s, 3H), 2.79 (t, 2H), 2.64 (d, 3H), 2.24 (t, 2H), 1.61-1.46 (m, 4H), 1.32-1.26 (m, 4H).

Example 149

N~9~-(4-chlorophenyl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-chloroaniline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 325, 327 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.53-8.47 (m, 1H), 7.61 (d, 2H), 7.33 (d, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 2.29 (t, 2H), 1.61-1.45 (m, 4H), 1.34-1.26 (m, 4H).

Example 150

N~1~-methyl-N~9~-(2-naphthyl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 2-aminonaphthalene for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 341 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.55-8.47 (m, 1H), 8.29 (br s, 1H), 7.85-7.77 (m, 3H), 7.59-7.55 (m, 1H), 7.48-7.35 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.35 (t, 2H), 1.66-1.57 (m, 2H), 1.51-1.47 (m, 2H), 1.34-1.28 (m, 4H).

Example 151

N~1~-methyl-2-oxo-N~9~-quinolin-3-ylnonanediamide

The desired product was prepared by substituting Example 124E and 3-aminoquinoline for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 342 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.95 (d, 1H), 8.75 (d, 1H), 8.54-8.47 (m, 1H), 7.98-7.93 (m, 2H), 7.70-7.64 (m, 1H), 7.62-7.57 (m, 1H), 2.81 (t, 2H), 2.64 (d, 3H), 2.40 (t, 2H), 1.69-1.58 (m, 2H), 1.56-1.45 (m, 2H), 1.48-1.39 (m, 4H).

Example 152

N~9~-(1,3-benzothiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 2-aminobenzothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 348 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.54-8.48 (m, 1H), 7.97-7.94 (m, 1H), 7.74-7.71 (m, 1H), 7.45-7.40 (m, 1H), 7.32-7.26 (m, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.50-2.45 (m, 2H), 1.65-1.56 (m, 2H), 1.55-1.45 (m, 2H), 1.33-1.26 (m, 4H).

Example 153

N~9~-(5-chloro-1,3-benzoxazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 5-chloro-2-aminobenzoxazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 366, 368 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.53-8.48 (m, 1H), 7.66-7.63 (m, 2H), 7.30 (dd, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.50-2.46 (m, 2H), 1.63-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 154

N~9~-(4-(4-chlorophenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4'-chlorophenyl)-2-aminothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 408, 410 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.53-8.47 (m, 1H), 7.90 (d, 2H), 7.66 (s, 1H), 7.48 (d, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.63-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 155

N~9~-(4-(4-bromophenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4'-bromophenyl)-2-aminothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 452, 454 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 12.22 (s,

1H), 8.53-8.47 (m, 1H), 7.84 (d, 2H), 7.67 (s, 1H), 7.62 (d, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.64-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.31-1.26 (m, 4H).

Example 156

N~9~~(4-(3-bromophenyl)-1,3-thiazol-2-yl)-N~1~~methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(3'-bromophenyl)-2-aminothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 452, 454 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.53-8.47 (m, 1H), 8.10-8.09 (m, 1H), 7.91-7.88 (m, 1H), 7.75 (s, 1H), 7.53-7.49 (m, 1H), 7.39 (t, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.64-1.56 (m, 2H), 1.54-1.44 (m, 2H), 1.32-1.26 (m, 4H).

Example 157

N-(8-(methylamino)-7,8-dioxooctyl)-1,1'-biphenyl-3-carboxamide

The desired product was prepared by substituting Example 142F and 3-phenylbenzoic acid for aniline and Example 1B, respectively, in Example 1C. MS (ESI(+)) m/e 367 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.59-8.48 (m, 2H), 8.10 (t, 1H), 7.84-7.79 (m, 2H), 7.81-7.75 (m, 2H), 7.57-7.48 (m, 3H), 7.43-7.38 (m, 1H), 3.31-3.24 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.58-1.46 (m, 4H), 1.35-1.26 (m, 4H).

Example 158

3-(4-(1,1'-biphenyl-4-yloxy)butoxy)-N-methyl-2-oxopropanamide

Example 158A

4-(1,1'-biphenyl-4-yloxy)butan-1-ol

A solution of ethyl 4-((1,1'-biphenyl)-4-yloxy)butanoate (3.3 g, 11.6 mmol, prepared by substituting ethyl 4-bromobutanoate for ethyl 7-bromoheptanoate in Example 2A) in dichloromethane (100 mL) at -78 °C was treated with 1M DIBAL in dichloromethane (35 mL, 35 mmol), warmed to room temperature over 2 hours, quenched with saturated sodium potassium tartrate, concentrated, and diluted with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to provide 2.8 g of the desired product. MS (ESI(+)) m/e 243 $(M+H)^+$.

Example 158B

4-(4-(2,2-diethoxyethoxy)butoxy)-1,1'-biphenyl

A solution of Example 158A (2.8 g, 11.5 mmol) in DMF (40 mL) at 0 °C was treated with 60% NaH dispersion in oil (0.508 g, 12.7 mmol), warmed to room temperature, stirred for 2 hours, cooled to 0 °C, and treated dropwise with bromoacetaldehyde diethyl acetal (2.09 mL, 13.9 mmol). The mixture was heated to 90 °C for 18 hours, cooled to room temperature, and partitioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 8:1 hexanes/ethyl acetate to provide 1.01g (24% yield) of the desired product. MS (ESI(+)) m/e 381 $(M+Na)^+$.

Example 158C

(4-(1,1'-biphenyl-4-yloxy)butoxy)acetaldehyde

A solution of Example 158B (1 g, 2.79 mmol) in 4:1 acetone/water (13 mL) was treated with conc. H_2SO_4 (9 drops), heated to reflux, stirred for 18 hours, cooled to room temperature, diluted with dichloromethane, washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 20:1 ethyl acetate/dichloromethane to provide the desired product as a mixture of aldehyde and hydrate. MS (DCI/NH_3) m/e 302 $(M+NH_4)^+$.

Example 158D

methyl 3-(4-(1,1'-biphenyl-4-yloxy)butoxy)-2-hydroxypropanoate

A suspension of Example 158C (100 mg, 0.35 mmol) in a mixture of water (1 mL) and THF (1 mL) at room temperature was treated with $NaHSO_3$ (57 mg) and KCN (34 mg), stirred for 18 hours, and concentrated under a stream of nitrogen. The resulting solid was collected by filtration and washed with cold water. The filter cake was dissolved in methanol (1 mL), cooled to 0 °C, treated with HBr gas for 1 hour, diluted with water (1 mL) and stirred for 30 minutes. The reaction was diluted with saturated $NaHCO_3$ and extracted three times with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was dissolved in methanol, stirred for 18 hours, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 1% methanol/dichloromethane to provide 80 mg (78% yield) of the desired product. MS (DCI/NH_3) m/e 362 $(M+H)^+$.

Example 158E

3-(4-(1,1'-biphenyl-4-yloxy)butoxy)-2-hydroxy-N-methylpropanamide

The desired product was prepared by substituting Example 158D for Example 101B in Example 101C.

Example 158F

3-(4-(1,1'-biphenyl-4-yloxy)butoxy)-N-methyl-2-oxopropanamide

The desired product was prepared by substituting Example 158E for Example 86A in Example 86B. MS (DCI/NH_3) m/e 342 $(M+H)^+$, 359 $(M+NH_4)^+$; ^{1}H NMR (DMSO-d_6) δ 8.64-8.59 (m, 1H), 7.62-7.57 (m, 4H), 7.42 (t, 2H), 7.30 (t, 1H), 7.03-7.00 (m, 2H), 4.69 (s, 2H), 4.04 (t, 2H), 3.52 (t, 2H), 2.64 (d, 3H), 1.82-1.76 (m, 2H), 1.73-1.66 (m, 2H); Anal. Cald for $C_{20}H_{23}NO_4 \cdot 0.125H_2O$: C, 69.90; H, 6.82; N, 4.08. Found: C, 69.91; H, 6.68; N, 3.90.

Example 159

N-(8-(methylamino)-7,8-dioxooctyl)-2-phenyl-1,3-thiazole-4-carboxamide

The desired product was prepared by substituting Example 142F and 2-phenyl-4-thiazole carboxylic acid for 4-aminopyridine and Example 1B, respectively, in Example 6. MS (ESI(+)) m/e 374 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.53-8.47 (m, 2H), 8.26 (s, 1H), 8.08-8.04 (m, 2H), 7.56-7.51 (m, 3H), 3.31-3.25 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.59-1.46 (m, 4H), 1.33-1.28 (m, 4H).

Example 160

5-(4-chlorophenyl)-N-(8-(methylamino)-7,8-dioxooctyl)-2-furamide

The desired product was prepared by substituting Example 142F and 5-(4-chlorophenyl)-2-furoic acid for 4-aminopyridine and Example 1B, respectively, in Example 6. MS (ESI(+)) m/e 391, 393 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.53-8.48 (m, 2H), 7.94 (d, 2H), 7.54 (d, 2H), 7.13 (s, 2H), 3.27-3.17 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.55-1.45 (m, 4H), 1.33-1.28 (m, 4H).

Example 161

1-benzyl-N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-3-carboxamide

The desired product was prepared by substituting Example 142F and 1-benzyl-3-indole carboxylic acid for 4-aminopyridine and Example 1B, respectively, in Example 6. MS (ESI(+)) m/e 420 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.53-8.46 (br m, 1H), 8.16-8.13 (m, 1H), 8.09 (s, 1H), 7.88-7.85 (br m, 1H), 7.50 (d, 1H), 7.36-7.22 (m, 5H), 7.20-7.09 (m, 2H), 5.45 (s, 2H), 3.26-3.19 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.56-1.46 (m, 4H), 1.35-1.28 (m, 4H).

Example 162

5-(benzyloxy)-N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting Example 142F and 5-benzyloxy-2-indole carboxylic acid for 4-aminopyridine and Example 1B, respectively, in Example 6. MS (ESI(+)) m/e 420 $(M-CH_3)^+$; ^1H NMR (DMSO-d_6) δ 11.37 (s, 1H), 8.53-8.48 (br m, 1H), 8.38-8.34 (br m, 1H), 7.49-7.46 (m, 2H), 7.42-7.30 (m, 4H), 7.16 (d, 1H), 6.99 (d, 1H), 6.90 (dd, 1H), 5.09 (s, 2H), 3.29-3.22 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.56-1.46 (m, 4H), 1.34-1.28 (m, 4H).

Example 163

N-(8-(methylamino)-7,8-dioxooctyl)benzamide

The desired product was prepared by substituting Example 142F and benzoic acid for 4-aminopyridine and Example 1B, respectively, in Example 6. MS (ESI(+)) m/e 291 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.54-8.48 (br m, 1H), 8.44-8.40 (br m, 1H), 7.84-7.81 (m, 2H), 7.51-7.41 (m, 3H), 3.27-3.20 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.54-1.66 (m, 4H), 1.32-1.27 (m, 4H).

Example 164

N~9~-(4-(4-cyanophenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-cyanophenyl)-2-aminothiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 399 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.28 (s, 1H), 8.53-8.48 (br m, 1H), 8.07 (d, 2H), 7.90 (s, 1H), 7.89 (d, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.63-1.46 (m, 4H), 1.32-1.26 (m, 4H).

Example 165

N~9~-(4-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2,3-dihydro-1-benzofuran-5-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 416 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.53-8.47 (br m, 1H), 7.75-7.74 (m, 1H), 7.65-7.62 (m, 1H), 7.36 (s, 1H), 6.79 (d, 1H), 4.56 (t, 2H), 3.21 (t, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.63-1.44 (m, 4H), 1.32-1.26 (m, 4H).

Example 166

N~1~-methyl-2-oxo-N~9~-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 428 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.54-8.48 (br m, 1H), 7.60-7.57 (m, 2H), 7.48 (s, 1H), 7.10-7.07 (m, 1H), 2.82-2.70 (m, 6H), 2.64 (d, 3H), 2.47-2.40 (m, 2H), 1.79-1.72 (m, 4H), 1.64-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.33-1.26 (m, 4H).

Example 167

N~9~-(4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 432 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.13 (s, 1H), 8.54-8.47 (br m, 1H), 7.43 (s, 1H), 7.37-7.34 (m, 2H), 6.88 (d, 1H), 4.26 (app s, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.63-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 168

N~9~-(4-(2,4-dimethoxyphenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2,4-dimethoxyphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 434 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.07 (s, 1H), 8.53-8.47 (br m, 1H), 7.97 (d, 1H), 7.44 (s, 1H), 6.66-6.60 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.63-1.45 (m, 4H), 1.32-1.25 (m, 4H).

Example 169

N~9~-(4-(2,5-dimethoxyphenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2,5-dimethoxyphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 434 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.54-8.47 (br m, 1H), 7.66-7.63 (m, 2H), 7.05 (d, 1H), 6.90-6.85 (m, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.47-2.42 (m, 2H), 1.62-1.46 (m, 4H), 1.31-1.26 (m, 4H).

Example 170

N~1~-methyl-2-oxo-N~9~-(4-(4-(trifluoromethyl)phenyl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(trifluoromethyl)phenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 442 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.28 (s,

1H), 8.53-8.48 (br m, 1H), 8.10 (d, 2H), 7.84-7.78 (m, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.65-1.44 (m, 4H), 1.32-1.26 (m, 4H).

Example 171

N~9~-(4-(1,1'-biphenyl-4-yl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(1,1'-biphenyl-4-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 450 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) d 12.22 (s, 1H), 8.53-8.48 (br m, 1H), 7.98 (d, 2H), 7.73-7.71 (m, 4H), 7.66 (s, 1H), 7.48 (t, 2H), 7.38-7.53 (m, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.66-1.46 (m, 4H), 1.32-1.27 (m, 4H).

Example 172

N~1~-methyl-2-oxo-N~9~-(4-(4-(trifluoromethoxy)phenyl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(4-(trifluoromethoxy)phenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 458 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.24 (s, 1H), 8.54-8.48 (br m, 1H), 8.00 (d, 2H), 7.68 (s, 1H), 7.42 (d, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.47 (t, 2H), 1.62-1.56 (m, 2H), 1.53-1.45 (m, 2H), 1.31-1.26 (m, 4H).

Example 173

N~1~-methyl-2-oxo-N~9~-(4-(3-(trifluoromethoxy)phenyl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(3-(trifluoromethoxy)phenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 458 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.24 (s, 1H), 8.53-8.47 (br s, 1H), 7.95-7.91 (m, 1H), 7.86-7.83 (m, 1H), 7.79 (s, 1H), 7.51 (t, 1H), 7.33-7.29 (m, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.62-1.57 (m, 2H), 1.53-1.46 (m, 2H), 1.31-1.27 (m, 4H).

Example 174

N~1~-methyl-2-oxo-N~9~-(4-(3,4,5-trimethoxyphenyl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(3,4,5-trimethoxyphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 464 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.21 (s, 1H), 8.53-8.48 (br m, 1H), 7.61 (s, 1H), 7.91 (s, 2H), 3.83 (s, 6H), 3.68 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.62-1.46 (m, 4H), 1.31-1.26 (m, 4H).

Example 175

N~1~-methyl-2-oxo-N~9~-(4-(4-phenoxyphenyl)-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(4-phenoxyphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 466 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.20 (s, 1H), 8.52-8.48 (br m, 1H), 7.89 (d, 2H), 7.52 (s, 1H), 7.44-7.39 (m, 2H), 7.20-7.14 (m, 1H), 7.08-7.03 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.64-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.31-1.26 (m, 4H).

Example 176

N~9~-(4-(4-(benzyloxy)phenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(benzyloxy)phenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 480 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.15 (s, 1H), 8.53-8.47 (br m, 1H), 7.82 (d, 2H), 7.48-7.33 (m, 6H), 7.06 (d, 2H), 5.14 (s, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.63-1.54 (m, 2H), 1.53-1.46 (m, 2H), 1.31-1.27 (m, 4H).

Example 177

N~1~-methyl-2-oxo-N~9~-(4-pyridin-3-yl-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(pyridin-3-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 375 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.27 (s, 1H), 9.11 (d, 1H), 8.52 (dd, 1H), 8.52-8.48 (br m, 1H), 8.24-8,20 (m, 1H), 7.78 (s, 1H), 7.46 (dd, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.65-1.56 (m, 2H), 1.54-1.45 (m, 2H), 1.32-1.27 (m, 4H).

Example 178

N~1~-methyl-2-oxo-N~9~-(4-pyridin-4-yl-1,3-thiazol-2-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 4-(pyridin-4-yl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 375 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.30 (s, 1H), 8.62 (d, 2H), 8.54-8.46 (br m, 1H), 7.96 (s, 1H), 7.83 (d, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.66-1.44 (m, 4H), 1.33-1.24 (m, 4H).

Example 179

N~9~-(4-(3-cyanophenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(3-cyanophenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 399 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.25 (s, 1H), 8.53-8,48

(br m, 1H), 8.31 (br s, 1H),8.21 (d, 1H), 7.84 (d, 1H), 7.78 (d, 1H), 7.65 (t, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.45 (t, 2H), 1.65-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 180

N~9~-(4-(4-ethoxyphenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-ethoxyphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 418 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.15 (s, 1H), 8.52-8.48 (br m, 1H), 7.79 (d, 2H), 7.41 (s, 1H), 6.96 (d, 2H), 4.09-4.02 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.64-1.46 (m, 4H), 1.34 (t, 3H), 1.31-1.26 (m, 4H).

Example 181

N~1~-methyl-N~9~-(4-(2-naphthyl)-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2-naphthyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 424 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.28 (s, 1H), 8.53-8.47 (br m, 1H), 8.42 (s, 1H), 8.06-8.03 (m, 1H), 7.97-7.90 (m, 3H), 7.75 (s, 1H), 7.75-7.49 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.46 (t, 2H), 1.67-1.46 (m, 4H), 1.33-1.28 (m, 4H).

Example 182

N~1~-methyl-N~9~-(4-(4-morpholin-4-ylphenyl)-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-morpholin-4-ylphenyl)-2-amino-1,3-thiazole for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 459 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 8.52-8.47 (br m, 1H), 7.74 (d, 2H), 7.36 (s, 1H), 6.98 (d, 2H), 3.76-3.73 (m, 4H), 3.17-3.13 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.63-1.47 (m, 4H), 1.31-1.26 (m, 4H).

Example 183

N-methyl-2-oxo-8-((4-phenyl-1,3-thiazol-2-yl)thio)octanamide

Example 183A

6-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)hexan-1-ol

The desired product was prepared by substituting 4-phenyl-1,3-thiazole-2-thiol and 6-bromohexanol for (1,1'-biphenyl)-4-ol and ethyl 7-bromoheptanoate, respectively, in Example 2A.

Example 183B

6-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)hexanal

The desired product was prepared by substituting Example 183A for Example 142A in Example 142B.

Example 183C

methyl (2Z)-2-((tert-butyl(dimethyl)silyl)oxy)-8-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)oct-2-enoate

The desired product was prepared by substituting Example 183B for Example 142B in Example 142C.

Example 183D

methyl 2-oxo-8-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)octanoate

The desired product was prepared by substituting Example 183C for Example 142C in Example 142D.

Example 183E

N-methyl-2-oxo-8-((4-phenyl-1,3-thiazol-2-yl)thio)octanamide

The desired product was prepared by substituting Example 183D for Example 106A in Example 106B. mp: 107-108 °C; MS (ESI(-)) m/e 361 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 8.50 (br s, 1H), 8.02 (s, 1H), 7.85-7.95 (m, 2H), 7.30-7.50 (m, 3H), 3.38 (t, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.20-1.80 (m, 8H); Anal. Calcd for: $C_{18}H_{22}N_2O_2S_2$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.59; H, 5.91; N, 7.44.

Example 184

8-(1,3-benzothiazol-2-ylthio)-N-methyl-2-oxooctanamide

Example 184A

6-(1,3-benzothiazol-2-ylsulfanyl)hexan-1-ol

The desired product was prepared by substituting 1,3-benzothiazole-2-thiol and 6-bromohexanol for (1,1'-biphenyl)-4-ol and ethyl 7-bromoheptanoate, respectively, in Example 2A.

Example 184B

6-(1,3-benzothiazol-2-ylsulfanyl)hexanal

The desired product was prepared by substituting Example 184A for Example 142A in Example 142B.

Example 184C

methyl (2Z)-8-(1,3-benzothiazol-2-ylsulfanyl)-2-((tert-butyl(dimethyl)silyl)oxy)oct-2-enoate

The desired product was prepared by substituting Example 184B for Example 142B in Example 142C.

Example 184D

methyl 8-(1,3-benzothiazol-2-ylsulfanyl)-2-oxooctanoate

The desired product was prepared by substituting Example 184C for Example 142C in Example 142D.

Example 184E

8-(1,3-benzothiazol-2-ylthio)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 184D for Example 106A in Example 106B. mp: 83-84 °C; MS (ESI(+)) m/e 336.9 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1H), 8.01 (dd, 1H), 7.85 (dd, 1H), 7.46 (dt, 1H), 7.47 (dt, 1H), 3.45 (m, 2H), 2.82 (t, 2H), 2.64 (d, 3H), 1.30-1.90 (m, 8H); Anal. Calcd for: $C_{16}H_{19}NO_3S_2$: C, 57.11; H, 5.99; N, 8.33. Found: C, 57.02; H, 5.89; N, 8.16.

Example 185

N-(8-(methylamino)-7,8-dioxooctyl)-4-phenyl-1,3-thiazole-2-carboxamide

The desired product was prepared by substituting Example 142F and 4-phenyl-2-thiazolecarboxylic for aniline and Example 1B, respectively, in Example 1C. MS (ESI(+)) m/e 374 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.88-8.84 (br m, 1H), 8.52-8.47 (br m,1H), 8.38 (s, 1H), 8.08 (d, 2H), 7.49 (t, 2H), 7.42-7.37 (m, 1H), 3.31-3.26 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.60-1.46 (m, 4H), 1.34-1.28 (m, 4H).

Example 186

N~9~-(1H-indol-5-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 5-aminoindole for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 330 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 10.94 (br s, 1H), 9.61 (br s, 1H), 8.52-8.46 (br m, 1H), 7.85 (d, 1H), 7.29-7.26 (m, 2H), 7.17 (dd, 1H), 6.34 (t, 1H), 2.80 (t, 2H), 2.64 (d, 3H), 2.27 (t, 2H), 1.62-1.46 (m, 4H), 1.32-1.28 (m, 4H).

Example 187

N~1~-methyl-2-oxo-N~9~-(3-phenyl-1,2,4-thiadiazol-5-yl)nonanediamide

The desired product was prepared by substituting Example 124E and 3-phenyl-1,2,4-thiadiazol-5-amine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+))

m/e 375 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 13.04 (s, 1H), 8.53-8.47 (br m, 1H), 8.17-8.14 (m, 2H), 7.53-7.49 (m, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 2.55 (t, 2H), 1.68-1.59 (m, 2H), 1.55-1.46 (m, 2H), 1.33-1.27 (m, 4H).

Example 188

N~1~-methyl-N~9~-(1-methyl-5-phenyl-1H-pyrazol-3-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 1-methyl-5-phenyl-1H-pyrazol-3-amine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 371 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.92 (br s, 1H), 8.53-8.47 (br m, 1H), 7.74 (d, 2H), 7.40-7.35 (m, 2H), 7.30-7.25 (m, 1H), 6.62 (s, 1H), 3.69 (s, 3H), 2.81 (t, 2H), 2.64 (d, 3H), 2.36 (t, 2H), 1.64-1.46 (m, 4H), 1.36-1.28 (m, 4H).

Example 189

N-methyl-2-oxo-8-((4-phenyl-1,3-thiazol-2-yl)sulfonyl)octanamide

The desired product was prepared by substituting Example 183 for Example 102D in Example 103. MS (ESI(-)) m/e 393 $(M-H)^-$; ^1H NMR (DMSO-d_6) δ 8.66 (s, 1H), 8.50 (br, 1H), 7.95-8.05 (m, 2H), 7.40-7.60 (m, 2H), 3.63 (t, 2H), 2.78 (t, 2H), 2.64 (d, 3H). Anal. Calcd for: $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.23; H, 5.53; N, 6.93.

Example 190

N~1~-methyl-N~9~-(4-(4-(2-morpholin-4-ylethoxy)phenyl)-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-(2-morpholin-4-ylethoxy)phenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 503 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.14 (s, 1H), 8.53-8.48 (br m, 1H), 7.80 (d, 2H), 7.42 (s, 1H), 6.99 (d, 2H), 4.12 (t, 2H), 3.59-3.56 (m, 4H), 2.80 (t, 2H), 2.70 (t, 2H), 2.64 (d, 3H), 2.49-2.46 (m, 4H), 2.43 (t, 2H), 1.64-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 191

N~1~-methyl-N~9~-(4-(6-morpholin-4-ylpyridin-3-yl)-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(6-morpholin-4-ylpyridin-3-yl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 460 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.66 (d, 1H), 8.53-8.48 (br m, 1H), 8.01 (dd, 1H), 7.43 (s, 1H), 6.89 (d, 1H), 3.79-3.62 (m, 4H), 3.50-3.47 (m, 4H), 2.80 (t, 2H), 2.64 (d, 3H), 2.43 (t, 2H), 1.62-1.44 (m, 4H), 1.31-1.25 (m, 4H).

Example 192

N~9~-(4-(4-(2-(dimethylamino)ethoxy)phenyl)-1,3-thiazol-2-yl)-N~1~-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-(2-(dimethylamino)ethoxy)phenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 461 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.14 (s, 1H), 8.53-8.47 (br m, 1H), 7.80 (d, 2H), 7.41 (s, 1H), 6.98 (d, 2H), 4.07 (t, 2H), 2.77 (t, 2H), 2.65-2.61 (m, 5H), 2.43 (t, 2H), 2.22 (s, 6H), 1.62-1.47 (m, 4H), 1.31-1.26 (m, 4H).

Example 193

N~1~-methyl-N~9~-(4-(4-(4-methylpiperazin-1-yl)phenyl)-1,3-thiazol-2-yl)-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(4-(4-methylpiperazin-1-yl)phenyl)-1,3-thiazol-2-amine for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 472 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.12 (s, 1H), 8.53-8.47 (br m, 1H), 7.72 (d, 2H), 7.33 (s, 1H), 6.96 (d, 2H), 3.19-3.16 (m, 4H), 2.79 (t, 2H), 2.64 (d, 3H), 2.47-2.40 (m, 6H), 2.23 (s, 3H), 1.62-1.47 (m, 4H), 1.31-1.27 (m, 4H).

Example 194

N-methyl-8-(((2-naphthylamino)carbonyl)amino)-2-oxooctanamide

A solution of 2-naphthylisocyanate (47 mg, 0.27 mmol) in dichloromethane (6 mL) at room temperature was treated with Example 142F (60 mg, 0.27 mmol) and triethylamine, (0.042 mL), stirred at room temperature for 2 hours, and partitioned between dichloromethane and 1N HCl. The organic phase was washed with brine, diluted with methanol, dried (Na_2SO_4), filtered, and concentrated to provide 34 mg of the desired product. MS (ESI(+)) m/e 356 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.60 (d, 1H), 8.01 (s, 1H), 7.79-7.68 (m, 3H), 7.36-7.46 (m, 2H), 7.27-7.34 (m, 1H), 6.21 (t, 1H), 3.10 (dt, 2H), 2.81 (t, 2H), 2.64 (d, 3H), 1.38-1.57 (m, 4H), 1.25-1.57 (m, 4H); Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.34; H, 6.91; N, 11.70.

Example 195

8-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)-N-methyl-2-oxooctanamide

Example 195A

methyl 7-((2-(4-methoxyphenyl)-2-oxoethyl)amino)-7-oxoheptanoate

The desired product was prepared by substituting 7-methoxy-7-oxoheptanoic acid and 2-amino-4'-methoxyacetophenone for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 322 $(M+H)^+$.

Example 195B

methyl 6-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)hexanoate

A solution of Example 195A (1.1 g, 3.43 mmol) in $CHCl_3$ (30 mL) was treated with P_2O_5 (3.89 g, 13.7 mmol), heated to reflux for 18 hours, cooled to room temperature, and partitioned between water and dichloromethane. The aquesous phase was extracted twice with dichloromethane and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by flash column chromatography with 1:1 hexanes/ethyl acetate to provide 0.71g (68% yield) of the desired product. MS (ESI(+)) m/e 304 $(M+H)^+$.

Example 195C

6-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)hexan-1-ol

The desired product was prepared by substituting Example 195B for ethyl 4-(1,1'-biphenyl)-4-yloxy)butanoate in Example 158A.

Example 195D

6-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)hexanal

The desired product was prepared by substituting Example 195C for Example 86A in Example 86B. MS (CI) m/e 274 $(M+H)^+$.

Example 195E

methyl 8-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)-2-oxooctanoate

The desired product was prepared by substituting Example 195D for Example 142B in Examples 142C and 142D. MS (ESI(+)) m/e 346 $(M+H)^+$.

Example 195F

8-(5-(4-methoxyphenyl)-1,3-oxazol-2-yl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 195E for Example 106A in Example 106B. MS (ESI(+)) m/e 345$(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 7.59(d, 2H), 7.36 (s, 1H), 7.02(d, 2H), 3.79 (s, 3H), 2.79 (t, 2H), 2.77 (t, 2H), 2.64 (d, 3H), 1.71 (m, 2H), 1.50 (m, 1H), 1.32 (m, 4H); Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.91; H, 6.92; N, 7.86.

Example 196

N-methyl-2-oxo-8-(2-phenyl-1,3-thiazol-4-yl)octanamide

Example 196A

methyl 8-bromo-7-oxooctanoate

A solution of 7-methoxy-7-oxoheptanoic acid (4.6 g, 26.6 mmol) in dichloromethane at room temperature (200 mL) was treated with oxalyl chloride (2.55 mL) and 1 drop of DMF, stirred for 1 hour, concentrated, and dissolved in diethyl ether (2 mL) to provide solution A. A mixture of diethyl ether (150 mL) and 40% aqueous KOH (45 mL) at 0 °C was treated portionwise with 1-methyl-3-nitro-1-nitrosoquanidine (15 g), and stirred for 10 minutes. The organic phase was dried over KOH, filtered, cooled to 0 °C, treated with solution A, stirred at 0 °C for 1.5 hours, treated with conc. HBr (33 mL), warmed to room temperature, and stirred for 30 minutes. The reaction was partitioned between water and ethyl acetate and the organic phase was washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to provide 5.69g (85% yield) of the desired product. MS (DCI) m/e 268, 270 $(M+NH_4)^+$.

Example 196B

methyl 6-(2-phenyl-1,3-thiazol-4-yl)hexanoate

A mixture of thiobenzamide (0.546g) and Example 196A 91 g, 3.98 mmol) in methanol (20 mL) at room temperature was stirred for 18 hours, concentrated, then partitioned between aq. $NaHCO_3$ and ethyl acetate. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 10% ethyl acetate/hexanes to provide 0.9g (78%)of the desired product. MS (ESI(+)) m/e 290 $(M+H)^+$.

Example 196C

6-(2-phenyl-1,3-thiazol-4-yl)hexanal

A -78 °C solution of Example 196B (0.7 g, 2.42 mmol) in dichloromethane (15 mL) was treated with 1M DIBAL in toluene (6.05 mL), stirred for 1 hour, treated with additional DIBAL (3 mL), stirred for 30 minutes, and quenced with methanol (0.7 mL) and Rochelle's salt. The reaction was warmed to room temperature and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purifed by flash column chromatography on silica gel with 20-30% ethyl acetate/hexanes to provide 0.47g (75%) of the desired product. MS (ESI(+)) m/e 260 $(M+H)^+$.

Example 196D

methyl (2Z)-2-((tert-butyl(dimethyl)silyl)oxy)-8-(2-phenyl-1,3-thiazol-4-yl)oct-2-enoate

The desired product was prepared by substituting Example 196C for Example 142B in Example 142C.

Example 196E

methyl 2-oxo-8-(2-phenyl-1,3-thiazol-4-yl)octanoate

The desired product was prepared by substituting Example 196D for Example 142C in Example 142D.

Example 196F

N-methyl-2-oxo-8-(2-phenyl-1,3-thiazol-4-yl)octanamide

The desired product was prepared by substituting Example 196E for Example 106A in 106B. mp: 70-72 °C; MS (ESI(+)) m/e 331 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.32-1.34 (m, 4H), 1.46-1.55 (m, 2H), 1.64-1.74 (m, 2H), 2.63-2.65 (d, 3H), 2.72-2.82 (m, 4H), 7.33 (s, 1H), 7.46-7.51 (m, 3H), 7.89-7.93 (m, 2H), 8.46-8.54 (br s, 1H); Anal. Calcd for: $C_{18}H_{22}N_2O_2S$ C, 65.43; H, 6.71; N, 8.48. Found: C, 65.27; H, 6.64; N, 8.26.

Example 197

8-((1,1'-biphenyl-4-ylsulfonyl)amino)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 142F and 4-phenylbenzenesulfonyl chloride for Example 143A and 4-chlorophenylsulfonyl chloride in Example 145. MS (ESI(-)) m/e 401 $(M-H)^-$; ^{1}H NMR (DMSO-d_6) δ 8.52-8.47 (br m, 1H), 7.90-7.83 (m, 4H), 7.73 (d, 2H), 7.62-7.58 (br m, 1H), 7.54-7.49 (m, 2H), 7.46-7.41 (m, 1H), 2.79-2.73 (m, 4H), 2.64 (d, 3H), 1.47-1.31 (m, 4H), 1.31-1.25 (m, 4H).

Example 198

7-((((1E)-1,1'-biphenyl-4-ylmethylidene)amino)oxy)-N-methyl-2-oxoheptanamide

Example 198A

1,1'-biphenyl-4-carbaldehyde oxime

A mixture of 4-phenylbenzaldehyde (3.64 g, 20 mmol), $NH_2OH{\cdot}HCl$ (2.72 g, 40 mmol) and pyridine (1 mL) in THF (20 mL) and ethanol (20 mL) was heated to reflux for 2 hours, cooled to room temperature, and concentrated. The residue was suspended in water and filtered. The filter cake was washed with water, and dried to provide 3.9g of the desired product. MS (ESI(+)) m/e 198 $(M+H)^+$.

Example 198B

1,1'-biphenyl-4-carbaldehyde O-(5-hydroxypentyl)oxime

The desired product was prepared by substituting Example 198A and 5-(t-butyldimethylsilyloxy)-pentyl bromide (1,1'-biphenyl)-4-ol and 6-(t-butyldimethylsilyloxy)-hexyl bromide, respectively, in Example 91A.

Example 198C

1,1'-biphenyl-4-carbaldehyde O-(5-oxopentyl)oxime

The desired product was prepared by substituting Example 198B for Example 142A in Example 142B.

Example 198D

methyl (2Z)-7-((((1E)-1,1'-biphenyl-4-ylmethylene)amino)oxy)-2-((tert-butyl(dimethyl)silyl)oxy)hept-2-enoate

The desired product was prepared by substituting Example 198C for Example 142B in Example 142C.

Example 198E

methyl 7-((((1E)-1,1'-biphenyl-4-ylmethylene)amino)oxy)-2-oxoheptanoate

The desired product was prepared by substituting Example 198D for Example 142C in Example 142D.

Example 198F

7-((((1E)-1,1'-biphenyl-4-ylmethylidene)amino)oxy)-N-methyl-2-oxoheptanamide

The desired product was prepared by substituting Example 198E for Example 106A in Example 106B. mp: 86-87 °C. MS (ESI(+)) m/e 353 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.52 (br s, 1H), 8.29 (s, 1H), 7.30-7.80 (m, 9H), 4.12 (t, 2H), 2.84 (t, 2H), 1.30-1.80 (m, 6H).

Example 199

N-methyl-2-oxo-8-(2-phenyl-1,3-oxazol-5-yl)octanamide

Example 199A

methyl 8-(bis(tert-butoxycarbonyl)amino)-7-oxooctanoate

A mixture of Example 196A (4.69 g, 18.7 mmol) and $(Boc)_2NK$ (5.24 g, prepared according to the procedure described in *J.Chem. Soc. Perkin Trans.* **1983**, 2983) in DMF (50 mL) was heated to 90 °C for 1 hour, then partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate twice and the combined extracts were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified

by flash column chromatography on silica gel with 20% ethyl acetate/hexanes to provide 6.57 g (91%) of the desired product. MS (ESI(+)) m/e 410 $(M+Na)^+$.

Example 199B

methyl 8-amino-7-oxooctanoate

A mixture of Example 199A (6.57 g) and 4N HCl in dioxane (20 mL) was stirred at room temperature for 1 hour, then diluted with diethyl ether. The precipitate was collected by filtration and the filter cake was dried to provide 3.22g (80%) of the desired product. MS (ESI(+)) m/e 188 $(M+H)^+$.

Example 199C

methyl 6-(2-phenyl-1,3-oxazol-5-yl)hexanoate

The desired product was prepared by substituting Example 199B and benzoic acid for aniline and Example 1B, respectively, in Example 1C.

Example 199D

methyl 6-(2-phenyl-1,3-oxazol-5-yl)hexanoate

The desired product was prepared by substituting Example 199C for Example 195A in Example 195B.

Example 199E

N-methyl-2-oxo-8-(2-phenyl-1,3-oxazol-5-yl)octanamide

The desired product was prepared by substituting Example 199D for Example 196B in Examples 196C and 196D. mp, 78-80 °C; MS (ESI(+)) m/e 315 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.26-1.40 (m, 4H), 1.46-1.55 (m, 2H), 1.60-1.70 (m, 2H), 2.63-2.65 (d, 3H), 2.70-2.75 (t, 2H), 2.78-2.82 (t, 2H), 7.01 (s, 1H), 7.45-7.54 (m, 3H), 7.91-7.94 (m, 2H), 8.5 (br s, 1H); Anal. Calcd for: $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.49; H, 7.01; N, 8.67.

Examples **200–215** were prepared in parallel using a Quest Apparatus. Each vessel was charged with 40 mg of Example 142F, 1.5 equivalents of the appropriate isocyanate (the isocyanates used are listed in each example), 0.043 mL of triethylamine and 3 mL of DMF. The reactions were mixed for 2 hours, then treated with PS-Trisamine resin (0.27 mmol), and mixed for an additional 2 hours. The reaction vessels were filtered and rinsed into scintillation vials and concentrated on a high speed vacuum centrifuge. The residues were then purified by preparative HPLC with a gradient system of 0 to 95% acetonitrile in water (containing 0.1% TFA) over 10 minutes to provide the desired products.

Example 200

8-((anilinocarbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: isocyanatobenzene. MS (ESI(+)) m/e 306 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.33 (s, 1H), 7.33-7.40 (m, 2H), 7.17-7.23 (m, 2H), 6.83-6.90 (m, 1H), 6.08 (t, 1H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.23-1.56 (m, 8H); Anal. Calcd for $C_{16}H_{23}N_3O_3 \cdot 0.25\ H_2O$: C, 62.02; H, 7.64; N, 13.56. Found: C, 62.12; H, 7.24; N, 13.58.

Example 201

N-methyl-8-((((2-methylphenyl)amino)carbonyl)amino)-2-oxooctanamide

Isocyanate: 1-isocyanato-2-methylbenzene. MS (ESI(+)) m/e 320 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.80 (d, 1H), 7.54 (s, 1H), 7.02-7.12 (m, 2H), 6.81-6.88 (m, 1H), 6.50 (t, 1H), 3.07 (dt, 2H), 2.81 (t, 2H), 2.65 (d, 3H), 2.16 (s, 3H), 1.25-1.57 (m, 8H);

Anal. Calcd for $C_{17}H_{25}N_3O_3 \cdot 0.25\ H_2O$: C, 63.04; H, 7.93; N, 12.97. Found: C, 63.37; H, 7.72; N, 12.97.

Example 202

N-methyl-8-((((3-methylphenyl)amino)carbonyl)amino)-2-oxooctanamide

Isocyanate: 1-isocyanato-3-methylbenzene. MS (ESI(+)) m/e 320 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.26 (s, 1H), 7.21 (s, 1H), 7.03-7.18 (m, 2H), 6.69 (d, 1H), 6.07 (t, 1H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.13 (s, 3H), 1.22-1.55 (m, 8H); Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.72; H, 7.69; N, 13.05.

Example 203

N-methyl-8-((((4-methylphenyl)amino)carbonyl)amino)-2-oxooctanamide

Isocyanate: 1-isocyanato-3-methylbenzene. MS (ESI(+)) m/e 320 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.22 (s, 1H), 7.21-7.28 (m, 2H), 7.00 (d, 2H), 6.02 (t, 1H), 3.04 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 2.20 (s, 3H), 1.22-1.56 (m, 8H); Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.55; H, 7.66; N, 12.95.

Example 204

8-((((2-methoxyphenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-2-methoxybenzene. MS (ESI(+)) m/e 336 $(M+H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.04-8.10 (m, 1H), 7.84 (s, 1H), 6.91-6.97 (m, 1H), 6.78-6.89 (m, 3H), 3.82 (s, 3H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.65 (d, 3H), 1.22-1.56 (m, 8H).

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.49; H, 7.31; N, 12.39.

Example 205

8-((((3-methoxyphenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-3-methoxybenzene. MS (ESI(+)) m/e 336 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (m, 1H), 8.38 (s, 1H), 7.06-7.15 (m, 2H), 6.83 (m, 1H), 6.45 (dd, 1H), 6.09 (t, 1H), 3.69 (s, 3H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.22-1.56 (m, 8H); Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.62; H, 7.32; N, 12.42.

Example 206

8-((((4-methoxyphenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-4-methoxybenzene. MS (ESI(+)) m/e 336 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (m, 1H), 8.16 (s, 1H), 7.27 (m, 2H), 6.79 (m, 2H), 5.99 (t, 1H), 3.68 (s, 3H), 3.03 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H, 5.1 Hz), 1.22-1.55 (m, 8H); Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.75; H, 7.21; N, 12.45.

Example 207

8-((((4-chlorophenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-4-chlorobenzene. MS (ESI(+)) m/e 340.7 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48-8.52 (m, 2H), 7.37-7.43 (m, 2H), 7.21-7.27 (m, 2H), 6.14 (t, 1H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.23-1.54 (m, 8H); Anal. Calcd for $C_{16}H_{22}N_3O_3Cl$: C, 56.55; H, 6.53; N, 12.37. Found: C, 56.50; H, 6.40; N, 12.33.

Example 208

8-((((3-bromophenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-3-bromobenzene. MS (ESI(+)) m/e 383.9, 385.9 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.53 (m, 1H), 7.81 (t, 1H), 7.12-7.23 (m, 2H), 7.01-7.07 (m, 1H), 6.20 (t, 1H), 3.05 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.23-1.55 (m, 8H).

Example 209

8-((((4-(dimethylamino)phenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

The desired product was prepared as the trifluoroacetate salt using 4-isocyanato-N,N-dimethylaniline. MS (ESI(+)) m/e 349.2 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (m, 1H), 8.40 (m, 1H), 7.32-7.41 (m, 2H), 7.02-7.21 (m, 2H), 6.10 (m, 1H), 2.93-3.10 (m, 8H), 2.80 (t, 2H), 2.44 (d, 3H), 1.22-1.55 (m, 8H); Anal. Calcd for $C_{18}H_{28}N_4O_3 \cdot CF_3CO_2H \cdot H_2O$: C, 49.99; H, 6.50; N, 11.66. Found: C, 49.96; H, 6.23; N, 11.61.

Example 210

N-methyl-2-oxo-8-((((3-(trifluoromethyl)phenyl)amino)carbonyl)amino)octanamide

Isocyanate: 1-isocyanato-3-trifluoromethylbenzene. MS (ESI(+)) m/e 374 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.53 (m, 1H), 7.97 (s, 1H), 7.39-7.51 (m, 2H), 7.21 (d, 1H), 6.26 (t, 1H), 3.07 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.23-1.55 (m, 8H).

Example 211

N-methyl-2-oxo-8-((((3-phenoxyphenyl)amino)carbonyl)amino)octanamide

Isocyanate: 1-isocyanato-3-phenoxybenzene. MS (ESI(+)) m/e 398 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.53 (m, 1H), 8.39 (s, 1H), 7.30-7.42 (m, 4H), 7.02-7.10 (m, 1H), 6.89-6.95 (m, 4H), 6.08 (t, 1H), 3.06 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.24-1.55 (m, 8H); Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.33; H, 6.80; N, 10.45.

Example 212

N-methyl-2-oxo-8-((((4-phenoxyphenyl)amino)carbonyl)amino)octanamide

Isocyanate: 1-isocyanato-4-phenoxybenzene. MS (ESI(+)) m/e 398 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (m, 1H), 8.38 (s, 1H), 7.30-7.42 (m, 4H), 7.02-7.09 (m, 1H), 6.88-6.95 (m, 4H), 6.08 (t, 1H), 3.06 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.25-1.56 (m, 8H); Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.35; H, 6.81; N, 10.49.

Example 213

8-(((1,1'-biphenyl-2-ylamino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 2-isocyanato-1,1'-biphenyl. MS (ESI(+)) m/e 382 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.52 (m, 1H), 7.87 (d, 1H), 7.01-7.52 (m, 9H), 6.54 (t, 1H), 3.00 (dt, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.20-1.53 (m, 8H).

Example 214

8-((((3,5-dimethoxyphenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 1-isocyanato-3,5-dimethoxybenzene. MS (ESI(+)) m/e 366.6 $(M+H)^+$; ^1H NMR (500 MHz, DMSO-d_6) δ 8.48 (m, 1H), 8.35 (s, 1H), 6.61 (m, 2H), 6.03-6.08 (m, 2H), 3.67 (s, 6H), 3.04 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.45-1.58 (m, 2H), 1.34-1.45 (m, 2H), 1.23–1.32 (m, 4H); Anal. Calcd for $C_{18}H_{27}N_3O_5$: C, 59.16; H, 7.45; N, 11.50. Found: C, 59.18; H, 7.06; N, 11.38.

Example 215

8-(((1,3-benzodioxol-5-ylamino)carbonyl)amino)-N-methyl-2-oxooctanamide

Isocyanate: 5-isocyanato-1,3-benzodioxole. MS (ESI(+)) m/e 350 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (m, 1H), 8.24 (s, 1H), 7.16 (m, 1H), 6.73-6.77 (m, 1H), 6.62-6.66 (m, 1H), 6.00 (m, 1H), 5.91 (s, 2H), 3.03 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.23-1.54 (m, 8H); Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N, 12.03. Found: C, 58.52; H, 6.28; N, 12.00.

Example 216

N~7~-methyl-7-oxo-N~1~,N~1~-diphenylheptane-1,1,7-tricarboxamide

Example 216A

di-tert-butyl 2-(5-((tert-butyl(dimethyl)silyl)oxy)pentyl)malonate

A suspension of 95% NaH oil dispersion (380 mg, 15 mmol) in THF (50 mL) at 0 °C was treated dropwise with di-tert-butyl malonate (2.65 mL, 11.8 mmol), warmed to room temperature over 30 minutes, treated with 5-(t-butyldimethylsilyloxy)pentyl bromide (3.30 g, 11.7 mmol), heated to reflux for 18 hours, and partitioned between water and diethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, concentrated and purified by flash column chromatography on silica gel with 2 to 3% ethyl acetate/hexanes to provide 1.66g (34%) of the desired product. MS (ESI(-)) m/e 415 $(M-H)^-$.

Example 216B

di-tert-butyl 2-(5-hydroxypentyl)malonate

A solution of Example 216A (1.66 g, 4.2 mmol) in THF (1 mL) was treated with 1M TBAF in THF (8.5 mL, 8.5 mmol), stirred for 3 hours, and partitioned between water and diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography on silica gel with 20% ethyl acetate/hexanes to provide 0.87 g (69%) of the desired product. MS (ESI(-)) m/e 301 $(M-H)^-$.

Example 216C

1,1-di-tert-butyl 7-methyl 7-oxoheptane-1,1,7-tricarboxylate

The desired product was prepared by substituting Example 216B for Example 142A in Examples 142B, 142C, and 142D.

Example 216D

di-tert-butyl 2-(7-(methylamino)-6,7-dioxoheptyl)malonate

The desired product was prepared by substituting Example 216C for Example 106A in Example 106B. MS (ESI(-)) m/e 370 $(M-H)^-$.

Example 216E

2-(7-(methylamino)-6,7-dioxoheptyl)malonic acid

A solution of Example 216C (0.516 g, 1.4 mmol) in HCOOH (16 mL) at room temperature was stirred for 8 hours and concentrated. The reaction was concentrated under a stream of nitrogen to provide 0.364g of the desired product. MS (ESI(-)) m/e 258 $(M-H)^-$.

Example 216F

N~7~-methyl-7-oxo-N~1~,N~1~-diphenylheptane-1,1,7-tricarboxamide

The desired product was prepared by substituting Example 216E for Example 1B in Example 1C. MS (ESI(+)) m/e 410 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 9.91 (s, 2H), 8.52-8.46 (br m, 1H), 7.60 (d, 4H), 7.31 (m, 4H), 7.05 (t, 2H), 3.49-3.45 (m, 1H), 2.79 (t, 2H), 2.63 (d, 3H), 1.94-1.85 (br m, 2H), 1.54-1.46 (m, 2H), 1.33-1.28 (m, 4H).

Example 217

8-(2-(4-bromophenyl)-1,3-oxazol-5-yl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting 4-bromobenzoic acid for benzoic acid in Example 199. mp: 90-92 °C; MS (ESI(+)) m/e 393, 395 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.27-1.41 (m, 4H), 1.43-1.57 (m, 2H), 1.57-1.70 (m, 2H), 2.63-2.65(d, 2H), 2.70-2.74 (t, 2H), 2.77-2.82 (t, 2H), 7.04 (1H), 7.70-7.73 (d, 2H), 7.84-7.87 (d, 2H), 8.50 (s, 1H); Anal. Calcd for: $C_{18}H_{21}BrN_2O_3$: C, 54.97; H, 5.38; N, 7.12. Found: C, 54.78; H, 5.46; N, 6.91.

Example 218

8-(2-(4-chlorophenyl)-1,3-thiazol-4-yl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting 4-chlorothiobenzamide for thiobenzamide in Example 196. mp: 77-81 °C; MS (ESI(+)) m/e 365, 367 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 1.23-1.40 (m, 4H), 1.45-1.55 (m, 2H), 1.63-1.73 (m, 2H), 2.63-2.65 (d, 3H), 2.72-2.82 (m, 4H), 7.37 (s, 1H), 7.53-7.56 (d, 2H), 7.91-7.94 (d, 2H), 8.49 (br s, 1H); Anal. Calcd for: $C_{18}H_{21}ClN_2O_2S$: C, 59.25; H, 5.80; N, 7.68. Found: C, 59.29; H, 5.86; N, 7.45.

Example 219

methyl 9-(1,1'-biphenyl-3-ylamino)-3-hydroxy-2,9-dioxononanoate

Example 219A

N-1,1'-biphenyl-3-yl-7-hydroxyheptanamide

The desired product was prepared by substituting 1,1'-biphenyl-3-amine and 8-hydroxyoctanoic acid for anilin and Example 1B, respectively in Example 1C.

Example 219B

N-1,1'-biphenyl-3-yl-7-oxoheptanamide

The desired product was prepared by substituting Example 219A for Example 142A in Example 142B.

Example 219C

methyl 9-(1,1'-biphenyl-3-ylamino)-3-hydroxy-2,9-dioxononanoate

The desired product was prepared by substituting Example 219B for Example 141A in Examples 141B, 141C, and 141D. MS (DCI) m/e 384 $(M+H)^+$, 401 $(M+NH_4)^+$; ^1H NMR (DMSO-d_6) δ 9.94 (s, 1H), 7.92 (br s, 1H), 7.61-7.55 (m, 3H), 7.47 (d, 2H), 7.40-7.29 (m, 3H), 6.82 (d, 1H), 4.20 (br d, 1H), 3.69 (s, 3H), 2.30 (t, 2H), 1.61-1.51 (m, 2H), 1.41-1.16 (m, 6H); Anal Calcd for $C_{22}H_{25}NO_5 \cdot 0.25H_2O$: C, 68.11; H, 6.63; N, 3.61. Found: C, 68.26; H, 6.55; N, 3.47.

Example 220

methyl 9-((4-(4-methoxyphenyl)-1,3-thiazol-2-yl)amino)-2,9-dioxononanoate

Example 220A

6-(1,3-dioxolan-2-yl)hexanoic acid

The desired product was by substituting methyl 6-(1,3-dioxolan-2-yl)hexanoate (prepared according to the procedure described in Syn. Comm. 1991, 1075) for Example 2A in Example 2B. MS (ESI(+)) m/e 189 $(M+H)^+$.

Example 220B

6-(1,3-dioxolan-2-yl)-N-(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)hexanamide

The desired product was prepared by substituting Example 220A and 4-(4'-methoxyphenyl)-2-aminothiazole for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 377 $(M+H)^+$.

Example 220C

N-(4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-7-oxoheptanamide

A solution of Example 220B (2.06 g, 5.47 mmol) in acetone (40 mL) and water (2 mL) was treated with p-toluenesulfonic acid monohydrate (30 mg), heated to reflux for 48 hours, cooled to room temperature, and diluted with water. The resulting precipitate was collected by filtration and dried to provide 1.3 g of the desired product. MS (ESI(+)) m/e 333 $(M+H)^+$.

Example 220D

methyl 9-((4-(4-methoxyphenyl)-1,3-thiazol-2-yl)amino)-2,9-dioxononanoate

The desired product was prepared by substituting Example 220C for Example 142B in Examples 142C and 142D. MS (ESI(+)) m/e 405 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 12.15 (s, 1H), 7.82 (d, 2H), 7.42 (s, 1H), 6.98 (d, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.81 (t, 2H), 2.43 (t, 2H), 1.62-1.46 (m, 4H), 1.32-1.27 (m, 4H).

Example 221

9-((4-(4-methoxyphenyl)-1,3-thiazol-2-yl)amino)-2,9-dioxononanoic acid

A suspension of Example 220 (96 mg, 0.24 mmol) in acetonitrile (3 mL) and water (1.5 mL) was treated with LiOH (11mg, 0.26 mmol), stirred at room temperature for 30 minutes, diluted with water, and acidified with 1N HCl. The resulting precipitate was collected by filtration to provide 78 mg (85% yield) of the desired product. MS (ESI(+)) m/e 391 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 14.50-13.20 (br s, 1H), 12.15 (s, 1H), 7.81 (d, 2H), 7.42 (s, 1H), 6.98 (d, 2H), 3.79 (s, 3H), 2.75 (t, 2H), 2.43 (t, 2H), 1.64-1.46 (m, 4H), 1.31-1.25 (m, 4H).

Example 222

N-(8-(methylamino)-7,8-dioxooctyl)-3-phenoxybenzamide

The desired product was prepared by substituting 3-phenoxybenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 383 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.53-8.44 (m, 2H), 7.63-7.59 (m, 1H), 7.49-7.39 (m, 4H), 7.19-7.13 (m, 2H), 7.05-7.02 (m, 2H), 3.24-3.18 (m, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.54-1.44 (m, 4H), 1.31-1.25 (m, 4H).

Example 223

N-(8-(methylamino)-7,8-dioxooctyl)-4-phenoxybenzamide

The desired product was prepared by substituting 4-phenoxybenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS

(ESI(+)) m/e 383 $(M+H)^+$; 1H NMR (DMSO-d_6) δ 8.53-8.48 (br m, 1H), 8.39-8.35 (m, 1H), 7.85 (d, 2H), 7.46-7.41 (m, 2H), 7.23-7.18 (m, 1H), 7.09-7.06 (m, 2H), 7.02 (d, 2H), 3.23 (q, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.55-1.44 (m, 4H), 1.32-1.26 (m, 4H).

Example 224

4-bromo-N-(8-(methylamino)-7,8-dioxooctyl)benzamide

The desired product was prepared by substituting 4-bromobenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 369, 371 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.53-8.47 (m, 2H), 7.77 (d, 2H), 7.66 (d, 2H), 3.26-3.19 (m, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.55-1.44 (m, 4H), 1.32-1.26 (m, 4H).

Example 225

3-bromo-N-(8-(methylamino)-7,8-dioxooctyl)benzamide

The desired product was prepared by substituting 3-bromobenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 369, 371 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.57-8.47 (m, 2H), 8.01-7.99 (m, 1H), 7.85-7.81 (m, 1H), 7.73-7.70 (m, 1H), 7.43 (t, 1H), 3.27-3.20 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.54-1.45 (m, 4H), 1.33-1.26 (m, 4H).

Example 226

N-(8-(methylamino)-7,8-dioxooctyl)-3-(methylsulfonyl)benzamide

The desired product was prepared by substituting 3-bromobenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. ^{1}H NMR (DMSO-d_6) δ 8.75-8.71 (br m, 1H), 8.53-8.47 (br m, 1H), 8.36-8.35 (m, 1H), 8.18-8.15 (m, 1H), 8.08-8.05 (m, 1H), 7.75 (t, 1H), 3.31-3.24 (m, 2H), 3.26 (s, 3H), 2.80 (t, 2H), 2.64 (d, 3H), 1.57-1.46 (m, 4H), 1.33-1.28 (m, 4H).

Example 227

N-(8-(methylamino)-7,8-dioxooctyl)-4-(1H-pyrrol-1-yl)benzamide

The desired product was prepared by substituting 4-(1H-pyrrol-1-yl)benzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. ^{1}H NMR (DMSO-d_6) δ 8.53-8.42 (m, 2H), 7.92 (d, 2H), 7.68 (d, 2H), 7.48-7.46 (m, 2H), 6.31-6.29 (m, 2H), 3.32-3.24 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.55-1.46 (m, 4H), 1.33-1.29 (m, 4H); Anal. Cald for $C_{17}H_{24}N_2O_5S \cdot 0.2CF_3COOH$: C, 53.42; H, 6.23; N, 7.16. Found: C, 53.05; H, 6.15; N, 6.74.

Example 228

1-methyl-N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-2-carboxamide

The desired product was prepared by substituting 1-methyl-1H-indole-2-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 344 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.53-8.43 (m, 2H), 7.62 (d, 1H), 7.51 (d, 1H), 7.29-7.23 (m, 1H), 7.11-7.06 (m, 1H), 7.04 (s, 1H), 3.97 (s, 3H), 3.27-3.20 (m, 2H), 2.81 (t, 2H), 2.64 (d, 3H), 1.58-1.48 (m, 4H), 1.35-1.29 (m, 4H).

Example 229

N-(8-(methylamino)-7,8-dioxooctyl)-2-naphthamide

The desired product was prepared by substituting 2-naphthoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 341 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.61-8.57 (m, 1H), 8.53-8.47 (br m, 1H), 8.43 (s, 1H), 8.03-7.90 (m, 4H), 7.63-7.56 (m, 2H), 3.33-3.27 (m, 2H), 2.81 (t, 2H), 2.64 (d, 3H), 1.60-1.48 (m, 4H), 1.36-1.30 (m, 4H).

Example 230

N-(8-(methylamino)-7,8-dioxooctyl)-1,3-benzodioxole-5-carboxamide

The desired product was prepared by substituting 1,3-benzodioxole-5-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 335 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.52-8.47 (br m, 1H), 8.25 (t, 1H), 7.42 (dd, 1H), 7.37 (d, 1H), 6.96 (d, 1H), 6.08 (s, 2H), 3.23-3.17 (m, 2H), 2.79 (t, 2H), 2.64 (d, 3H), 1.54-1.42 (m, 4H), 1.31-1.25 (m, 4H).

Example 231

N-(8-(methylamino)-7,8-dioxooctyl)-1-benzofuran-2-carboxamide

The desired product was prepared by substituting 1-benzofuran-2-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 331 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.68 (t, 1H), 8.52-8.47 (br m, 1H), 7.76 (d, 1H), 7.66-7.63 (m, 1H), 7.51-7.50 (m, 1H), 7.48-7.43 (m, 1H), 7.35-7.30 (m, 1H), 3.29-3.22 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.58-1.46 (m, 4H), 1.34-1.28 (m, 4H).

Example 232

N-(8-(methylamino)-7,8-dioxooctyl)-1H-benzimidazole-6-carboxamide

The desired product was prepared by substituting 1H-benzimidazole-6-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 331 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 9.02 (br s, 1H), 8.59-8.47 (m, 2H),

8.21-8.20 (m, 1H), 7.90 (dd, 1H), 7.77 (d, 1H), 3.31-3.24 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.58-1.47 (m, 4H), 1.34-1.28 (m, 4H).

Example 233

N-(8-(methylamino)-7,8-dioxooctyl)-1H-indole-6-carboxamide

The desired product was prepared by substituting 1H-benzimidazole-6-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 330 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 11.34 (s, 1H), 8.53-8.48 (br m, 1H), 8.33-8.29 (br m, 1H), 7.92 (s, 1H), 7.57-7.47 (m, 3H), 6.48-6.46 (m, 1H), 3.28-3.22 (m, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.56-1.47 (m, 4H), 1.35-1.28 (m, 4H).

Example 234

3-chloro-N-(8-(methylamino)-7,8-dioxooctyl)benzamide

The desired product was prepared by substituting 3-chlorobenzoic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 325/327 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.57-8.48 (m, 2H), 7.87-7.86 (m, 1H), 7.81-7.77 (m, 1H), 7.60-7.57 (m, 1H), 7.49 (t, 1H), 3.24 (q, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.55-1.46 (m, 4H), 1.32-1.26 (m, 4H).

Example 235

4-methyl-N-(8-(methylamino)-7,8-dioxooctyl)-2-(4-(trifluoromethyl)phenyl)-1,3-thiazole-5-carboxamide

The desired product was prepared by substituting 4-methyl-2-(4-(trifluoromethyl)phenyl)-1,3-thiazole-5-carboxylic acid and Example 142F for Example 1B and 4-aminopyridine, respectively, in Example 6. MS (ESI(+)) m/e 456 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.53-8.47 (br m, 1H), 8.35-8.32 (m, 1H), 8.15 (d, 2H), 7.88 (d, 2H), 3.26-3.19 (m, 2H), 2.81 (t, 2H), 2.64 (d, 3H), 2.62 (s, 3H), 1.56-1.47 (m, 4H), 1.34-1.28 (m, 4H).

Example 236

N^1-methyl-2-oxo-N^8-(4-phenyl-1,3-thiazol-2-yl)octanediamide

Example 236A

8-(methylamino)-7,8-dioxooctanoic acid

The desired product was prepared by substituting methyl 5-hydroxypentanoate for methyl 6-hydroxyhexanoate in Examples 124A through 124E.

Example 236B

N^1-methyl-2-oxo-N^8-(4-phenyl-1,3-thiazol-2-yl)octanediamide

The desired product was prepared by substituting Example 236A and 4-phenyl-2-aminothiazole for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 369 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H), 8.53-8.48 (br m, 1H), 7.89 (d, 2H), 7.59 (s, 1H), 7.45-7.40 (m, 2H), 7.34-7.29 (m, 1H), 2.81 (t, 2H), 2.64 (d, 3H), 2.44 (t, 2H), 1.66-1.47 (m, 4H), 1.35-1.27 (m, 2H).

Example 237

N^9-(4-(2,5-dimethylthien-3-yl)-1,3-thiazol-2-yl)-N^1-methyl-2-oxononanediamide

The desired product was prepared by substituting Example 124E and 4-(2,5-dimethylthien-3-yl)-1,3-thiazol-2-amine for Example 1B and aniline, respectively, in Example 1C. MS (ESI(+)) m/e 408 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 12.06 (s, 1H), 8.52-8.47 (br m, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 2.79 (t, 2H), 2.64 (d, 3H), 2.56 (s, 3H), 2.43 (t, 2H), 2.38 (s, 3H), 1.63-1.45 (m, 4H), 1.32-1.26 (m, 4H).

Example 238

N-methyl-2-oxo-8-(5-thien-2-yl-1,3,4-oxadiazol-2-yl)octanamide

Example 238A

N-methyl-2,9-dioxo-9-(2-(thien-2-ylcarbonyl)hydrazino)nonanamide

A solution of Example 124E (0.1 g, 0.46 mmol) in N,N-dimethylformamide (15 mL) at room temperature was treated with polystyrene supported dicyclohexylcarbodiimide (0.48 g, 0.9 mmol), hydroxybenzotriazole (0.06 g, 0.46 mmol) and thiophene-2-carbohydrazide (0.06 g, 0.46 mmol), stirred for 8 hours, and filtered. The resin was washed with DMF (5 mL) and dichloromethane (5 mL) and the combined washes and filtrate were evaporated to provide the desired product.

Example 238B

N-methyl-2-oxo-8-(5-thien-2-yl-1,3,4-oxadiazol-2-yl)octanamide

A solution of Example 238A in THF (5 mL) was treated with (methoxycarbonylsulfamoyl)-triethyl ammonium hydroxide (0.22 g, 0.96 mmol), irradiated in a Smith microwave synthesizer at 300 W for 15 minutes, and concentrated. The concentrate was dissolved in 1:1 DMSO:CH_3OH (1.5 mL) and purified by reverse phase HPLC with a gradient of 0 to 95% acetnitrile/water containing 0.1% TFA over 10 minutes to provide the desired product (0.045 g, 31%). MS (ESI(+)) m/e 322 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.5 (s, 1H), 7.90 (d, 1H), 7.78 (d, 1H), 7.30 (t, 1H), 2.90 (t, 2H), 2.80 (t, 2H), 2.60 (d, 3H), 1.78 (m, 2H), 1.50 (m, 2H), 1.2-1.4 (m, 4H).

Example 239

N-methyl-2-oxo-8-(5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)octanamide

The desired product was prepared by substituting 3,4,5-trimethoxybenzohydrazide for thiophene-2-carbohydrazide in Example 238. MS (ESI(+)) m/e 406 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.5 (s, 1H), 7.20 (s, 2H), 3.90 (s, 6H), 3.70 (s, 3H), 2.90 (t, 2H), 2.80 (t, 2H), 2.60 (d, 3H), 1.78 (m, 2H), 1.50 (m, 2H), 1.2-1.4 (m, 4H).

Example 240

9-(2-benzoylhydrazino)-N-methyl-2,9-dioxononanamide

The desired product was prepared by substituting benzohydrazide for thiophene-2-carbohydrazide in Example 238A. MS (ESI(+)) m/e 334 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 10.3 (s, 1H), 9.8 (s, 1H), 8.5 (s, 1H), 7.90 (d, 2H), 7.50 (m, 1H), 7.40 (d, 2H), 2.80 (t, 2H), 2.60 (d, 3H), 2.20 (t, 2H), 1.4-1.6 (m, 4H), 1.2-1.4 (m, 4H).

Example 241

9-(2-(1,1'-biphenyl-4-ylcarbonyl)hydrazino)-N-methyl-2,9-dioxononanamide

The desired product was prepared by substituting 1,1'-biphenyl-4-carbohydrazide for thiophene-2-carbohydrazide in Example 238A. MS (ESI(+)) m/e 410 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 10.3 (s, 1H), 9.8 (s, 1H), 8.5 (s, 1H), 8.00 (d, 2H), 7.80 (d, 2H), 7.78 (d, 2H), 7.50 (m, 2H), 7.40 (m, 1H), 2.80 (t, 2H), 2.60 (d, 3H), 2.20 (t, 2H), 1.4-1.6 (m, 4H), 1.2-1.4 (m, 4H).

Example 242

8-(5-(1,1'-biphenyl-4-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting Example 241 for Example 238A in Example 238B. MS (ESI(+)) m/e 392 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ 8.5 (s, 1H), 8.02 (m, 2H), 7.90 (m, 2H), 7.78 (m, 2H), 7.50 (m, 2H), 7.40 (m, 1H), 2.90 (t, 2H), 2.80 (t, 2H), 2.60 (d, 3H), 1.78 (m, 2H), 1.50 (m, 2H), 1.2-1.4 (m, 4H).

Example 243

8-((((4-(benzyloxy)phenyl)amino)carbonyl)amino)-N-methyl-2-oxooctanamide

The desired product was prepared by substituting 1-isocyanato-4-benzyloxybenzene for isocyanatobenzene in Example 200. MS (ESI(+)) m/e 412 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (m, 1H), 8.15 (s, 1H), 7.22-7.45 (m, 7H), 6.84-6.91 (m, 2H), 5.98 (t, 1H), 5.02 (s, 2H), 3.04 (dt, 2H), 2.80 (t, 2H), 2.64 (d, 3H), 1.22-1.55 (m, 8H); Anal. Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 67.26; H, 7.10; N, 10.11.

Example 244

7-(1,1'-biphenyl-4-yloxy)-1-(2H-tetraazol-5-yl)heptan-1-one

Example 244A

8-(1,1'-biphenyl-4-yloxy)-2-(tetrahydro-2H-pyran-2-yloxy)octanenitrile

A solution of Example 112C (0.92 g, 2.94 mmol) and dihydropyran (0.247 g, 2.94 mmol) in dichloromethane (100 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (56 mg, 0.29 mmol), stirred for 5 hours, and partitioned between water and dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel to provide 1.04 g (90% yield) of the desired product. MS (DCI/NH_3) m/e 393 $(M+H)^+$.

Example 244B

5-(7-(1,1'-biphenyl-4-yloxy)-1-(tetrahydro-2H-pyran-2-yloxy)heptyl)-2H-tetraazole

A mixture of example 244B (150 mg, 0.38 mmol), sodium azide (49 mg, 0.76 mmol), and NH_4Cl (41 mg, 0.76 mmol) in DMF (2 mL) was heated to reflux for 5 hours, cooled to room temperature, and partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 3% methanol/dichloromethane to provide 80 mg (48% yield) of the desired product. MS (DCI/NH_3) m/e 437 $(M+H)^+$.

Example 244C

7-(1,1'-biphenyl-4-yloxy)-1-(2H-tetraazol-5-yl)heptan-1-ol

A solution of Example 244B (60 mg) in methanol (5 mL) at room temperature was treated with p-toluenesulfonic acid monohydrate (10mg), stirred for 3 hours, poured into ice water, and filtered. The filter cake was dried to provide 40 mg (83%) of the desired product. MS (ESI(+)) m/e 353 $(M+H)^+$.

Example 244D

7-(1,1'-biphenyl-4-yloxy)-1-(2H-tetraazol-5-yl)heptan-1-one

A solution of Example 244C (30 mg) in acetone (2 mL) at room temperature was treated dropwise with Jones reagent until a red-brown color persisted. The reaction mixture was filtered and the filtrate was partitioned between water and ethyl acetate. The organic extract was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated to provide 20 mg (60% yield) of the desired product. MS (DCI/NH3(+)) m/e 368 $(M+NH_4)^+$; ^1H NMR

(300 MHz, DMSO-d_6) δ 7.70-7.50 (m, 4H), 7.50-7.35 (m, 2H), 7.30-7.20 (m, 1H), 7.05-6.90 (m, 2H), 3.98 (t, 2H), 3.00 (t, 2H), 1.80-1.20 (m, 8H).

Example 245

7-(1,1'-biphenyl-3-yloxy)-1-(2H-tetraazol-5-yl)heptan-1-one

Example 245A

8-(1,1'-biphenyl-3-yloxy)-2-hydroxyoctanenitrile

The desired product was prepared by substituting 7-((1,1'-biphenyl)-3-yloxy)heptanal for Example 112B in Example 112C.

Example 245B

7-(1,1'-biphenyl-3-yloxy)-1-(2H-tetraazol-5-yl)heptan-1-one

The desired product was prepared by substituting Example 245A for Example 112C in Example 244. MS (DCI/NH3(+)) m/e 368 $(M+NH_4)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70-7.10 (m, 8H), 7.00-6.90 (m, 1H), 4.02 (t, 2H), 3.08 (t, 2H), 1.80-1.30 (m, 8H).

Example 246

N-1,1'-biphenyl-3-yl-7-oxo-7-(2H-tetraazol-5-yl)heptanamide

Example 246A

N-1,1'-biphenyl-3-yl-6-(1,3-dioxolan-2-yl)hexanamide

The desired product was prepared by substituting 1,1'-biphenyl-3-amine and 6-(1,3-dioxolan-2-yl)hexanoic acid (prepared according to the procedure described in Syn. Comm. **1991**, *21*, 1075) for aniline and Example 1B, respectively, in Example 1C. MS (ESI(+)) m/e 340 $(M+H)^+$.

Example 246B

N-1,1'-biphenyl-3-yl-7-oxoheptanamide

A solution of Example 246A (2.5 g, 7.4 mmol) in acetone (20 mL) and water (10 mL) was treated with p-toluenesulfonic acid monohydrate (70 mg), heated to reflux for 2 days, cooled to room temperature, treated with 2N HCL (2 mL), stirred for 1 hour, and partitioned between water and ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 20% ethyl acetate/hexanes to provide 1.5 g of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.68 (t, 1H), 7.95 (s, 1H), 7.70-7.2 (m, 8H), 2.45 (dt, 2H), 2.34 (t, 2H), 1.7-1.2 (m, 6H).

Example 246C

N-1,1'-biphenyl-3-yl-7-cyano-7-hydroxyheptanamide

The desired product was prepared by substituting Example 246B for Example 112B in Example 112C.

Example 246D

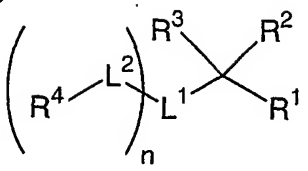
N-1,1'-biphenyl-3-yl-7-oxo-7-(2H-tetraazol-5-yl)heptanamide

The desired product was prepared by substituting Example 246C for Example 112C in Example 244. MS (ESI (+)) m/e 364 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.96 (t, 1H), 7.70-7.2 (m, 8H), 2.38 (dt, 2H), 2.34 (t, 2H), 1.8-1.3 (m, 6H).

It will be evident to one skilled in the art that the present invention is not limited to the forgoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims and therefore intended to be embraced therein.

WHAT IS CLAIMED IS

1. A compound of formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

n is 1 or 2;

L^1 is selected from the group consisting of alkenylene, alkylene, alkynylene, cycloalkylene, heteroalkylene, -(alkylene)-C(O)N(R^5)-(alkylene)-, -(alkylene)-O-(alkylene)-; wherein each group is drawn with its left-hand end being the end which attaches to L^2, and its right-hand end being the end which attaches to the carbon substituted with R^1, R^2, and R^3;

L^2 is selected from the group consisting of a bond, C_2 alkenylene, -O-, -S-, -SO_2-, -OC(O)NR^5-, -N(R^6)C(O)-, -C(O)N(R^6)-, -SO_2N(R^6)-, -N(R^6)SO_2-, -C=N-O-, -N(R^6)C(O)N(R^6)-, and -C(O)N(R^6)N(R^6)C(O)-; wherein each group is drawn with its left-hand end being the end which attaches to R^4, and its right-hand end being the end which attaches to L^1;

R^1 is selected from the group consisting of alkanoyl, alkoxycarbonyl, aminocarbonyl, carboxy, haloalkyl, and heterocycle, wherein the heterocycle is selected from the group consisting of oxazolyl, dihydrooxazolyl, oxadiazolyl, and tetraazolyl;

R^2 and R^3 are hydroxy; or

R^2 and R^3 together are oxo;

R^4 is selected from the group consisting of alkoxyalkyl, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle, and (heterocycle)alkyl; and

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, and arylalkyl; or

R^4 and R^6, together with the nitrogen atom to which they are attached, form a heterocycle selected from the group consisting of morpholinyl, piperazinyl, piperidinyl, and thiomorpholinyl; wherein the morpholinyl, the piperazinyl, the piperidinyl, and the thiomorpholinyl can be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl and spiroheterocycle.

2. A compound according to Claim 1 wherein n is 2.

3. A compound according to Claim 1 wherein n is 1.

4. A compound according to Claim 3 wherein R^1 is heterocycle, wherein the heterocycle is selected from the group consisting of oxazolyl, dihydrooxazolyl, oxadiazolyl, and tetraazolyl.

5. A compound according to Claim 4 wherein L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

6. A compound according to Claim 3 wherein R^1 is selected from the group consisting of alkoxycarbonyl and carboxy.

7. A compound according to Claim 6 wherein L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

8. A compound according to Claim 3 wherein R^1 is alkanoyl.

9. A compound according to Claim 8 wherein L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

10. A compound according to Claim 3 wherein R^1 is aminocarbonyl.

11. A compound according to Claim 10 wherein L^1 is -(alkylene)-O-(alkylene)-.

12. A compound according to Claim 10 wherein L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

13. A compound according to Claim 12 wherein L^2 is selected from the group consisting of -O-, -S-, -SO_2-, and -$SO_2N(R_6)$-.

14. A compound according to Claim 12 wherein L^2 is selected from the group consisting of -$N(R^6)C(O)N(R^6)$- and -$C(O)N(R^6)$-.

15. A compound according to Claim 12 wherein L^2 is selected from the group consisting of a bond, -C=N-O-, and -$N(R^6)C(O)CHC(O)N(R^5)(R^6)$-.

16. A compound according to Claim 12 wherein L^2 is -$N(R^6)C(O)$-.

17. A compound according to Claim 12 wherein L^2 is selected from the group consisting of $-N(R^6)C(O)N(R^6)-$ and $-C(O)N(R^6)N(R^6)C(O)-$.

18. A compound according to Claim 3 wherein R^1 is haloalkyl.

19. A compound according to Claim 18 wherein L^1 is selected from the group consisting of alkenylene, wherein the alkenylene is C_6 alkenylene; alkynylene, wherein the alkynylene is C_6 alkynylene; cycloalkylene; and -(alkylene)$C(O)N(R^5)$(alkylene)-.

20. A compound according to Claim 18 wherein L^1 is alkylene, wherein the alkylene is C_5-C_7 alkylene.

21. A compound according to Claim 20 wherein L^2 is C_2 alkenylene.

22. A compound according to Claim 20 wherein L^2 is $-OC(O)N(R^5)-$.

23. A compound according to Claim 20 wherein L^2 is -O-.

24. A compound according to Claim 20 wherein L^2 is $-N(R^6)C(O)-$.

25. A compound according to Claim 24 wherein R^4 is selected from the group consisting of alkoxyalkyl and alkyl.

26. A compound according to Claim 24 wherein R^4 is aryl.

27. A compound according to Claim 24 wherein R^4 is arylalkyl.

28. A compound according to Claim 24 wherein R^4 is selected from the group consisting of cycloalkyl, heterocycle, and (heterocycle)alkyl.

29. A compound according to Claim 24 wherein R^4 and R^6, together with the nitrogen atom to which they are attached, form a ring selected from the group consisting of morpholinyl, piperazinyl, piperidinyl, and thiomorpholinyl.

30. A pharmaceutical composition comprising a compound of Claim 1, or a therapeutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

31. A method of inhibiting histone deacetylase in a patient in recognized need of such treatment comprising administering to the patient a therapeutically acceptable amount of a compound of Claim 1, or a therapeutically acceptable salt thereof.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: Compounds having the formula or therapeutically acceptable salts thereof, are histone deacetylase (HDAC) inhibitors. Preparation of the compounds, compositions containing the compounds, and treatment of diseases using the compounds are disclosed.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 01/50931

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/14 C07C235/16 C07C235/20 C07C235/74 C07C235/80
C07C255/54 C07C255/60 C07D295/10 C07C243/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MANFRED JUNG ET AL: "Amide Analogues of Trichostatin A as Inhibitors of Histone Deacetylase and Inducers of Terminal Cell Differentiation" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 22, 4 November 1999 (1999-11-04), pages 4669-4679, XP002144226 ISSN: 0022-2623 page 4669, column 1, line 1 -page 4671, column 2, line 30 --- -/--	1,30,31

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2002	22/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 01/50931

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SUZUKI ET AL: "Synthesis and Histone Deacetylase Inhibitory Activity of New Benzamide Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 15, 1999, pages 3001-3003, XP002158227 ISSN: 0022-2623 the whole document	1,30,31

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 01/50931

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1 - 31 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 - 31 (all in part)

Present claims 1 to 31 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.